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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

FIFTEENTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 1, 2, AND 3, 1900.

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Page 428, Fig. 3. By an error of the engraver, instead of a fac-simile reproduction of the chest-tracing as called for by the text, a diagrammatic copy is here given. In consequence both outlines are incorrectly drawn, and the enlargement is unfortunately considerably exaggerated. A correct tracing will be found in the article as printed in the *American Journal of the Medical Sciences* for January, 1901.

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FIFTEENTH ANNUAL MEETING,

Held in Washington, D. C., May 1, 2, *and* 3, 1900.

THE following members were present during the meeting

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J. F. A. Adams,
I. Adler,
L. F. Barker,
H. M. Biggs,
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A. D. Blackader,
J. W. Brannan,
Norman Bridge,
S. C. Busey,
R. C. Cabot,
Charles Cary,
S. Solis-Cohen,
Wm. T. Councilman,
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R. T. Edes,
J. S. Ely,
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S. A. Fisk,
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Simon Flexner,
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M. H. Fussell,
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H. A. Hare,
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James C. Wilson,
C. F. Withington,
H. Wood,
J. H. Wright.

TUESDAY, MAY 1ST.

The Association was called to order at 10.10 A.M. by President Janeway, who delivered the following INTRODUCTORY ADDRESS:

For the fifteenth time it devolves upon the President to welcome the members of the Association to that gathering which has its chief interest in meeting those engaged in like work. We will hear from them that which, during the year past, has seemed of all that they have met and observed, the most fit to bring before colleagues interested in learning some new fact as regards the old diseases, or some new interpretation of the phenomena of those maladies.

Fortunately, we also have amongst our members those who are able to give themselves up to the study of pathology, and from whom, in the past, we have learned much of the pathological processes which underlie diseases, who will at this meeting continue their good work. Of late we have also been fortunate in having members who have given anxious thought to the chemical side of the study of the alterations of disease, and who will again strive to enlighten us on this the most difficult of the questions with which we have to do. Each of us who has attended the past meetings must admit having received much of benefit from the presentations and the discussion of our associates.

Your President of this year looks back with regret at certain of the opportunities which he wasted in the past, under the stress of his professional work, and he only alludes to it in passing that he may stimulate the younger members to so arrange the year that they may find the time to both give and receive knowledge, thus making the meetings of this Association more valuable with each passing year. Let us each endeavor to make this Association, so far as in us lies, as regards those matters which it falls under our province to consider, the equal of any and the inferior to none throughout the world. If we are each possessed by such a noble spirit of rivalry I am sure that our Association will not only maintain, but will surpass in the future that high regard in which it has been held.

Your President, in the fear that not enough of the members would bring material, sent out, as you know, two appeals. Results show that he was not sufficiently aware of the deep interest which you had in the success of our meeting in this the year of the Medical Congress. The calendar, as you have read, is more than full, and in so far as he may have been responsible for this, the motto that "brevity is the soul of wit" is forced home upon his inner consciousness. It is his duty as well

as his privilege to so allot the time that each member may be heard, and not himself to consume such time by his general introductory remarks as to infringe upon that which is the moral right of the member under the circumstances. But for this he would have been tempted to touch upon the theme—Truth in Medicine. This could have been handled under such heads as truth in statistics, truth in diagnosis, truth in therapeutics, truth in pathology.

Any society which has its annual meetings in the City of Washington, a city named after a man whose name could stand as a synonym for truth, should, so far as its members are concerned, need no other reminder of the value of truth; nor do I think that the members of this Association need even this reminder, for I take it we are all seekers after truth.

Would that all who come to Washington could be so impressed by his name that only the truth should be spoken in this city, or only honest methods followed in the pursuit of power, place, and gain.

We mourn this year that two of our old associates can no more participate in these meetings—each has been conquered by death, whose ravages they have so long attempted to avert for others. I allude to our original member, J. E. Graham, of Toronto, Canada, and to D. W. Prentiss, of Washington, D. C., who joined in 1888. It would be a pleasant memento if we should send a note of sympathy to those relatives who mourn the loss of noble men, our former associates.

But time urges, and we now turn to the work of the Association.

The Secretary read the names of those nominees that had been recommended by the Council for election, and also a communication from Dr. W. W. Keen, President of the American Medical Association, in regard to the bill (Senate Bill No. 34) to prohibit vivisection in the District of Columbia.

It was resolved, on motion of Dr. Kinnicutt, seconded by Dr. Sternberg, that,

"WHEREAS, The Antivivisection Bill, now designated as Senate Bill No. 34, has been again introduced into Congress by Senator Gallinger, the Association of American Physicians hereby renews its protest against the enactment of the bill."

Drs. Wm. H. Welch, A. C. Abbott, and W. W. Johnston were appointed a committee to contest the passage of the bill.

It was resolved, on motion of Dr. F. C. Shattuck, seconded by Dr. Sternberg, that "The President of this Association be authorized and directed to execute on behalf of the Association a petition to the Congress of the United States, asking for relief of charitable, religious, and

educational institutions from the provisions of the war revenue act of 1898, by which a tax is imposed on legacies left to such institutions."

The Treasurer then read his annual report, which was referred to an Auditing Committee, consisting of Drs. Cary and Northrup

Dr. James B. Herrick read a paper on "Casts in the Urine during Diabetic Coma," and one on "The Occasional Low Specific Gravity of Diabetic Saccharine Urine," which were not discussed.

Dr. James J. Putnam read a paper by himself, and Dr. F. Pfaff read one entitled "Communication on the Relation of Uric-acid Secretion to Epileptic Attacks," which was not discussed.

Dr. Charles G. Stockton read a paper entitled "Report of a Case of Acute Ascending Paralysis Showing Hæmatoporphyrinuria," which was discussed by Drs. Putnam and Janeway.

Dr. A. C. Abbott read a paper entitled "The Relative Infrequency of Acute Transmissible Diseases during the First Year of Childhood, with a Discussion of the Probable Reasons for the Same," which was discussed by Drs. Trudeau and G. B. Shattuck.

Dr. J. P. C. Griffith read a paper entitled "Recurrent Vomiting in Childhood," which was discussed by Drs. Stockton, Johnston, Kinnicutt, Forchheimer, F. C. Shattuck, and Griffith.

Dr. E. L. Trudeau read a paper entitled "Sanitarium Treatment of Pulmonary Tuberculosis, and its Results," which was discussed by Drs. Bridge, Cohen, and Trudeau.

The Secretary read a paper by Dr. Herter entitled "The Origin of Oxaluria from Fermentation in the Gastro-enteric Tract," which was discussed by Dr. Tyson.

Dr. Kinnicutt exhibited a specimen of "Acute Phlegmonous or Suppurative Gastritis," which was discussed by Drs. Welch and Janeway.

Adjourned at 12.40 P.M.

WEDNESDAY, MAY 2D.

The Association was called to order at 10.10 A.M. by President Janeway.

The following nominees, recommended by the Council, were elected members of the Association:

Drs. L. E. Holt, Henry Koplik and James Ewing, of New York; Dr. George G. Sears, of Boston; Dr. F. G. Novy, of Ann Arbor, and Dr. Henry Sewall, of Denver.

Dr. J. H. Wright gave a lantern-slide exhibition of "The Organism and Lesions of Actinomycosis." A number of lantern-slides were shown with the aid of the stereopticon. These were designed to illus-

trate the morphology and cultural characteristics of actinomycosis and also the histology of the lesions produced by this parasite in the various organs and tissues of the human body. Attention was called to the fact that probably many cases of human actinomycosis go unrecognized.

Dr. Hektoen gave a lantern-slide exhibition of "A New Pathogenic Fungus (Sporothrix of Schenck)." These papers were discussed by Drs. Flexner, Da Costa, and Hektoen.

Dr. Cabot read a paper entitled "Some Conclusions Arrived at After a Study of One Hundred and Ten Cases of Pernicious Anæmia."

Dr. Billings read a paper entitled "Report of Cases of Pernicious Anæmia, with Special Reference to the Blood Findings."

Dr. Henry read a paper entitled "Clinical Notes on Cases of Pernicious Anæmia." These papers were discussed by Drs. Cabot, Kinnicutt, Hare, Thomson, McPhedran, Mitchell, Stockton, Thayer, Da Costa, Herrick, and Henry.

Dr. Mallory read a paper entitled "Proliferation and Phagocytosis," which was discussed by Drs. Welch and Mallory.

Dr. Thayer read a paper entitled "A Report of Two Cases of Chronic Diarrhœa Associated with the Presence of the Strongylus Intestinalis (Anguillula Steroralis)," which was discussed by Drs. Cabot and Styles (by invitation).

Adjourned at 1.20 P.M.

THURSDAY, MAY 3D—MORNING SESSION.

The Association was called to order at 10.10 A.M. by President Janeway.

Dr. Councilman read a paper, written by Drs. Lothrop and Pratt, entitled "Case of Filariæ, with Specimens of the Adult Parasite," which was not discussed.

Dr. Park read a paper entitled "The Elimination of Deleterious Substances from Antitoxic Sera," which was discussed by Drs. Peabody, Meltzer, and Park.

Dr. Wesbrook read a paper, prepared by himself in collaboration with Drs. Wilson and McDaniel, entitled "Further Studies on the Morphology of Bacillus Diphtheriæ," which was discussed by Drs. Abbott, Park, and Wesbrook.

The Auditing Committee reported they had examined the Treasurer's report and vouchers, and found them to be correct.

Dr. Johnston presented a case of "Addison's Disease under Treatment with Suprarenal Extract."

Dr. Welch read a paper entitled "Venous Thrombosis as a Complica-

tion of Cardiac Disease," which was discussed by Drs. Kinnicutt, Cary, and Welch.

Dr. Flexner read a paper entitled "The Nature of the New Tissue in Cirrhosis of the Liver, and its Distribution," which was discussed by Dr. Shattuck.

Dr. Fitz read a paper entitled "Cystoma of the Pancreas," which was not discussed.

Dr. Cary read a paper entitled "Degenerated Echinococcus Cysts of the Pleura," which was discussed by Dr. Vickery.

Dr. Stengel read a paper entitled "Aneurism of the Aorta, with Rupture into the Superior Vena Cava, Recognized during Life," which was not discussed.

Dr. Robinson read a paper entitled "Minor Forms of Cardiac Dilatation," which was not discussed.

Adjourned at 1.15 P.M.

AFTERNOON SESSION.

The Association was called to order at 2.40 P.M. by President Janeway.

Dr. Thomson read a paper entitled "Graves' Disease without Exophthalmic Goitre," which was discussed by Drs. Edes, Thomson, Janeway, McPhedran, and Thomson.

Dr. Fussell read a paper entitled "Perichondritis of the Larynx in Typhoid Fever, with Exhibition of a Patient and a Specimen," which was not discussed.

Dr. Hare read a paper entitled "The Attitude of the Physician and Surgeon to Appendicular Symptoms Complicating Typhoid Fever," which was not discussed.

Dr. Van Gieson read a paper entitled "Observations on Appendicitis," which was not discussed.

Dr. Bridge read a paper entitled "Observations on Human Temperature in Disease," which was not discussed.

Dr. J. K. Mitchell read a paper entitled "Study of a Mummy Affected with Infantile Paralysis," which was not discussed.

Dr. Edes exhibited "A New Modified Sphygmograph."

During the meeting the following papers were read by title:

"An Experimental and Clinical Study of Acid Intoxications," by C. A. Herter.

"The Existence of Bacteria in Normal Tissues," by J. G. Adami, for W. Ford, of Montreal.

"Subpectoral Abscess," by J. H. Musser.

"Stone in the Kidney, and Conditions Simulating It," by D. D. Stewart.

"Graves' Disease without Exophthalmic Goitre," by D. D. Stewart.

"The Circular Fibres of the Heart (Mitral Sphincter) as a Factor in Functional Disturbances of the Heart with Mitral Insufficiency," by Morton Prince.

"Would it Not be a Gain both to Pathology and Practice if a Direct Interaction between the Morbific Agent (Noxa) and the Reparative Effort were Recognized, and the Conception of an Intermediate, So-called Inflammatory Process Abandoned?" by A. H. Smith.

"The History of a Case of Circumscribed Scleroderma," by S. B. Ward.

"Clinical Types of Uric-acid Diathesis; Treatment" (completion of paper), by I. N. Danforth.

"Sarcoma of the Stomach," by George Dock.

"A Case of Multiple Fibromas of the Nerves, with Arthritis Deformans," by L. Hektoen and R. B. Preble.

"Multiple Myeloma," by J. H. Wright.

"The Urea Content of the Blood in Cases of Nephritis," by J. S. Thacher.

"A Study of Twenty-four Cases of Typhoid Fever with Symptoms of Peritoneal Infection; Laparotomy," by F. C. Shattuck, for G. B. Shattuck, J. C. Warren, and F. Cobb, Committee of Boston Society of Medical Improvement.

The following officers were elected:

President—Wm. H. Welch.
Vice-President—H. P. Walcott.
Secretary—Henry Hun.
Treasurer—J. P. Crozer Griffith.
Recorder—I. Minis Hays.
Councillor—W. W. Johnston.

It was resolved that the Secretary be directed to convey to the Cosmos Club the thanks of the Association for the use of the hall in which the meetings had been held.

It was resolved that the thanks of the Association be tendered to President Janeway for his efforts and labors to promote the success of the meeting, which have been so brilliantly crowned with success.

It was resolved that the sum of twenty-five dollars be appropriated from the treasury to help defray the expenses of the American Committee of the Thirteenth International Medical Congress.

Adjourned at 4.30 P.M.

HENRY HUN,
Secretary.

PAPERS.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

NOTES ON DIABETES.

By JAMES B. HERRICK, M.D,
OF CHICAGO.

1. On Casts in the Urine during Diabetic Coma.

A small amount of albumin and a few casts are not uncommon in the urine of many—according to some, of most—cases of diabetes mellitus. Cardiovascular changes or uræmic symptoms may give evidence of a true chronic diffuse or chronic interstitial nephritis, and explain the persistence of albumin and casts. During or just preceding diabetic coma, however, casts may suddenly appear in such extraordinary numbers as to deserve mention. E. Külz[1] and Aldehoff[2] were the first to notice this phenomenon. Sandmeyer made a report on it in 1891 to the Tenth Congress of Internal Medicine. Mering, Rumpf,[3] Nebelthau,[4] and Williamson confirmed it. It had been previously noticed that in some cases of diabetic coma casts were present, but it was apparently regarded as accidental. Since my attention was called to this phenomenon by reading Williamson's[5] work I have seen it in all of three cases where I have sought for it. If the urine obtained as coma approaches be allowed to stand for a few hours, a light, hazy, grayish or slightly yellowish sediment will be seen at the bottom of the sediment glass, rising, perhaps, to one-sixth the height of the urine. The same sediment is, of course, obtainable by means of the centrifuge. This sediment will be found to consist almost entirely of short, broad, light-colored, finely granular casts. There is no relation

[1] C. Külz, Inaug. Dis., Marburg, 1895, reports ten cases of E. Külz's in which this phenomenon was observed.
[2] Aldehoff, in Külz's Klinische Erfahrungen ueber Diabetes Mellitus, Jena, 1899, p. 458.
[3] Rumpf. Ueber Diabetes Mellitus, Berl. klin. Woch., 1895, No. 31.
[4] Nebelthau. Berl. klin. Woch., 1896, No. 34.
[5] Williamson. Diabetes Mellitus and Its Treatment. Edinburgh, 1898, pp. 178 and 286.

between the amount of albumin and the number of these casts. In several cases Williamson watched the urine carefully for days before the onset of the coma, but no deposit was seen until just before the symptoms of coma commenced. The casts may appear twenty-four hours in advance of coma and thus give warning of its approach. In cases of coma with recovery, casts have been known to make their appearance with the manifestations of coma, and have disappeared as the symptoms have vanished. Aldehoff[1] has seen them appear within three hours in the urine of a diabetic who returned from a fatiguing walk, with a rapid pulse, oppression in the chest, labored, deep breathing—in short, what seemed to Aldehoff as threatening coma. The urine contained numerous "coma-casts." The urine passed three hours before had been free from such casts. The patient recovered and the casts disappeared.

The cases I have examined were as follows:

CASE I.—A man, aged sixty-five years, seen with Dr. Wynekoop. He had not consulted a physician for years until a few days before, when he had gone to Dr. Wynekoop, who found sugar, the first knowledge of the existence of diabetes. Questioning, however, revealed the fact that the subjective symptoms of diabetes dated back for more than a year. When I saw him coma was advancing. Urine was obtained by the catheter, and showed, in addition to the ordinary findings of the urine of diabetic coma, the sediment of finely granular casts above described. In this case, a large drop of urine being examined with a low power, and no cover-glass being used, they were seen piled against and across one another like sticks in a loose woodpile. There was but a trace of albumin. Death occurred in less than twenty-four hours after the specimen was obtained.

CASE II.—An old lady, aged eighty-four years, whose husband had died of diabetes seven years before, consulted me because of sleeplessness and mental depression. There were thirst, weakness, and furuncles. Sugar was abundant in the urine. Three weeks later a fatal coma developed. Enormous numbers of granular and hyaline casts were present, as in the previous case; albumin was but slight in amount.

CASE III.—In a third case, seen with Dr. Pigall, a woman of about sixty years, who had been told three years before that she had sugar in the urine, became dull, dyspnœic, had several convulsions, followed by coma and death. There was no paralysis. The urine was loaded with sugar and albumin and contained very large numbers of casts. This may be an instance of uræmic coma or a mixture of the uræmic and diabetic.

[1] Aldehoff. Loc. cit.

This phenomenon may, as Aldehoff and Williamson claim, be of value in the early diagnosis of coma. With suspicious symptoms it might well be a confirmatory test, and it might enable the physician, by early treatment, to secure at least a temporary recovery. Naunyn, while admitting the presence of casts during coma, is rather skeptical regarding their occurrence in the enormous numbers Külz described, and especially as to their frequent appearance in the prodromal stage.[1] Even though later investigation may show that in other forms of coma there may be similar casts, the value in the early recognition of diabetic coma is not lessened. Upon just what pathological condition it depends is unknown. It is possible or even probable that the kidneys during coma are overpowered by the attempt to eliminate some toxic substance, be it acetone, diacetic acid, or oxybutyric acid, and that there are rapid changes in the kidneys, such as have been noted by many observers, especially the fatty degeneration and the alterations in the loop of Henle, and that because of these renal changes cylindruria results. As Rumpf expresses it, there is a destruction of the secreting epithelium that in the elimination of the toxic products of tissue-change suddenly gives way.

2. On the Occasional Low Specific Gravity of Saccharine Diabetic Urine.

The specific gravity of the urine in diabetes generally rises with the amount of urine and the percentage of sugar. So true is this that, given the specific gravity and the amount of urine, approximate quantitative estimate of the sugar can be made by empirically constructed tables. Yet the specific gravity of the sugar-containing urine may be so influenced that it is lowered below the average of saccharine urine or even that of normal urine. A close study of cases of diabetes shows that at times diabetics may pass urine that contains sugar and that has a specific gravity as low as 1020, or much less. This does not include the polyuria with low specific gravity that sometimes precedes diabetic glycosuria or persists after convalescence and after sugar has disappeared. Polyuria may occur because of the development of a chronic interstitial nephritis, in which case the urine will

[1] Naunyn. Diabetes Mellitus, p. 293. Nothnagel's System.

show albumin and casts, but will at the same time contain sugar and be of lower specific gravity. In fact, some go so far as to say that when in diabetes mellitus the specific gravity falls below 1020 one should always suspect the beginning of an interstitial nephritis. In these cases later the sugar may be reduced to a minimum or entirely disappear. Thus, April 26, 1900, I examined a man, fifty-four years of age, with typical history of thirst, excessive appetite, emaciation, weakness, polyuria, and glycosuria. He was then on diabetic treatment by his physician. His total urine for twenty-four hours was 1500 c.c.; specific gravity, 1012. It contained a trace of sugar, albumin, and a few granular casts. There was beginning consolidation of the right apex. Here the nephritis apparently lowered the specific gravity.

Strümpell says that in those who are very weak the specific gravity may fall below 1020.

The drinking of large amounts of water or other liquid may lower the specific gravity in a marked manner. A patient of mine, fifty-eight years of age, with well-marked diabetes, drank large quantities daily of a mineral water of supposed curative properties. The specific gravity of the urine for days was never over 1019, and was often 1015 to 1018, yet the test for sugar was always strongly positive. Another patient, a fleshy man, aged fifty-five years, under observation for nearly a year, with typical manifestations of diabetes of the obese adult, came into my office one day partially intoxicated, and soon asked for a urinal. He passed about twenty-four ounces of urine, which I immediately tested for sugar. There was a prompt reaction. The specific gravity of the specimen tested by different urinometers, and by another physician as well as myself, was 1004. The patient had been drinking beer with some friends all the morning, an explanation of the intoxication, the polyuria, and the low specific gravity.

On looking up the subject I find that even lower specific gravities than this are reported as occasionally met with. In one of Külz's series of 224 cases, 27, or 12 per cent., showed at times a specific gravity of less than 1010. In one case it was as low as 1003. Eichhorst says that once in a while a specific gravity as low as 1008 or 1002 is seen. The latter case is perhaps the one Waterman reported in the *New York Medical Record* in 1882. Naunyn found a specific gravity of 1003 in spite of over 1 per cent. of sugar; and many

other cases with occasional specific gravities below 1010 are reported. The lesson is, therefore, plain that the only safe way is to examine every urine for sugar, even that of low specific gravity. One patient may be in the incipient stage of a complicating chronic nephritis, may be weak and debilitated, or may have been consuming large amounts of liquids, any one of which circumstances may tend to lower the specific gravity of the sugar-containing urine. And the importance of this fact to the life insurance examiner needs no elucidation. That some companies to-day require the examiner to test for sugar only when the specific gravity is above 1020, or perhaps 1015, shows that the occasional occurrence of saccharine urine of low specific gravity is not as freely recognized as it should be.

REPORT OF A CASE OF ACUTE ASCENDING PARALYIS, SHOWING HÆMATOPORPHYRINURIA.

By CHARLES G. STOCKTON, M.D.,
OF BUFFALO.

THE patient, aged twenty-seven years, was a domestic. Her father, when past middle age, died of some unknown cause, the mother and one brother of tuberculosis; three sisters are alive and well. Previous to the past two years the patient had lived for six years in the family of a physician, and it is known that she was well and strong. For two years past she had overworked and felt that she was losing her health. She had decreased twenty pounds in weight, but there was no specific disease. About a year ago she had obstipation of the bowels, and at one time went without an evacuation for fourteen days. In the early part of August last she became nervous and irritable, and was so anæmic that her employer requested Dr. Albert E. Woehnert to examine her. The girl appeared to be hysterical, and the other servants complained that she disturbed them. At night she tossed about in sleep and arose tired in the morning. Although she complained of a disagreeable taste, the appetite was good, tongue clean, and bowels regular. The pulse was 80 and the temperature 99.2°. Simple nervines were administered and her temperature carefully recorded morning and evening for a week. The highest point reached was 99.4°. The urine was of a very dark color, acid, free from sugar, contained a trace of albumin, and was microscopically negative. Alkalies, alteratives, and nervines were given. The girl went into the country and returned on the 28th of August somewhat improved, having gained several pounds in weight, and declared that she was much better. On the 4th of September she was feeling well, but still complained of a disagreeable taste in the mouth.

On September 7th she came to the doctor's office and complained of pain in the back and abdomen. She was again nervous and was now unable to sleep. He prescribed sodium salicylate and sulphonal, three doses of five grains each; but these were vomited. Next day she was no better and had not slept. On September 29th the patient was still sleepless, nervous, and the pain in the back continued. Pulse ranged between 50 and 64. She had vomited a little and the bowels were constipated; the urine was of claret color, 1025 specific gravity, contained neither albumin nor sugar; indican, a small trace; it was highly acid, and negative microscopically.

The patient was sent to the Riverside Hospital, where she remained for one week, during which time she was restless, slept little—not at all during the first three days—and complained of her stomach. Sulphonal (15 grains) the first night, and trional (15 grains) the second night, failed. These drugs thereafter were not given, and some rest was obtained from morphine and the bromides. Asafœtida and valerian were also administered, and, apparently, with benefit. On the 14th of September, against the protests of the hospital, she went home, where her temperature was still carefully taken. It showed but little variation, and the patient's condition could not be explained. Incipient tuberculosis was suspected. Physical examination of the chest showed, on inspection, equal and good expansion on both sides, anteriorly and posteriorly. The vocal fremitus was normal, slightly greater in the upper right chest. On percussion, the note was slightly higher pitched in the same region; posteriorly there was no difference. On auscultation, the expiration was prolonged in the right supraclavicular and infraclavicular regions. There were no râles, although faint crackling was heard at the left apex. The first sound of the heart was weak, and the second pulmonic sound was over-accentuated. The physical signs were otherwise normal. The liver and spleen were of normal size; the lower border of the stomach was two inches below the xiphoid. The stomach contents, examined two and one-half hours after a breakfast of finely chopped beefsteak with stale roll and butter, showed three ounces of well-digested contents, with free HCl, 0.05 per cent., total acidity 80, and a good biuret reaction, some undigested starch, no lactic acid, good motion and good absorption. At this time were passed 700 c.c. of urine in twenty-four hours—acid, claret color, 1020 specific gravity, a trace of albumin and indican, but no sugar, and it was negative microscopically. The further examination of the abdomen showed that it was not distended, nor tender on pressure. She had an excited and apprehensive appearance; her pupils were dilated; she was very nervous and slept only when under the influence of morphine or the bromides. The urine continued of a claret color. The patient occasionally seemed to wander in her mind. She said she had no sensation in the buttocks when sitting down. This region was found to be anæsthetic. She soon defecated and urinated unconsciously and involuntarily.

The patient was so excited and restless at home that on September 18th she was sent to the Buffalo General Hospital, a diagnosis not having been made. When she entered the hospital she gave a history of stomach trouble dating from the middle of August. After eating she had experienced gastric distress, accompanied by eructations of gas and a feeling of weakness and dizziness, and said that two weeks ago she was taken suddenly with a dull pain in the back, and now complained of a feeling of numbness and tingling in the feet. She said that this feeling had been experienced for several days, and at the same time she had lost strength and appetite. She now had weakness in her legs and involuntary and unconscious evacuations of the bladder and bowels; she did not feel the moisture. In the past twenty-four hours she

had occasional shooting pains in the legs. On entrance she felt as though she were losing her speech; was tired and sleepy, although unable to sleep. The temperature was 101.5° and the pulse 110. The following day she had little sensation or motion in the legs, and the deep and superficial reflexes were absent. On September 20th all sensation and motion had disappeared from the lower extremities; both motion and sensation of the trunk and upper extremities were much diminished. She was clear mentally, but frightened. The urine had the same claret color, although she had taken neither sulphonal nor trional for over a week.

On September 21st she was, at my request, examined by Dr. James W. Putnam, at which time there was found slight voluntary movement of the extensor muscles of the arm only. The deep and superficial reflexes were absent, and there was no response to the faradic current in the legs. There was slight electrical response in the extensor muscles of the arms and wrists, better on the right than on the left side. Sensation in the extremities and trunk had practically disappeared. On the 22d the area of diminished sensation extended upward to the level of the neck, but she had now regained the power to reflex both feet slightly; she could not move the upper extremities at all. At times she was slightly delirious. On the 23d the motions of the feet were more noticeable; there were none in the hands; she had become somewhat dull mentally, but was rational when roused, and complained only of being tired, and frequently asked to have the position of the arms and legs changed. The temperature was 106° F., the pulse 135, and the respirations 35.

On September 21st, Dr. Lorenzo Burrows, Jr., made an ophthalmoscopic examination, which showed that on the nasal side of both optic disks there were swelling and congestion, the vessels being slightly tortuous, and the condition was believed to be the beginning of optic neuritis. On the 24th there was no change noticed in the condition of the eyes. On this date there was undoubtedly improved motion in the feet, and the patellar reflexes could be faintly excited.[1] There was complete loss of motion of the arms; she was unable to feel in the breast the large hypodermatic needle used in introducing subcutaneously the normal salt solution; she was practically without sensation except in the head. The mind wandered slightly, but she responded rationally to all questions. Toward evening she complained of compression in the chest, making it difficult to breathe. At 11.30 P.M. she complained of thirst and drank eagerly. The pulse was 135 and the temperature 100° F. She said she felt well, only that she was "so tired." Her consciousness was perfect until immediately before 12.15 P.M., when she died quietly.

The clinical diagnosis was that of acute ascending myelitis, involving all the tracts of the cord. The treatment was limited to the use of normal salt solutions subcutaneously, and diaphoresis by means of baths. Sleep was encouraged on two or three occasions by small doses of codein. An autopsy was positively refused.

[1] There is a possible error in this observation.

A remarkable feature of the case was the persistance of the claret-colored urine. When first observed the color was dark amber or brown. After three doses, containing each five grains of sodium salicylate and sulphonal (which, by the way, were believed to have been vomited), the urine was noticed to be claret color, and it continued so to the end. A specimen was referred to Dr. Thomas B. Carpenter, clinical pathologist of the hospital, who made the following report on the coloring matter: "Methæmoglobin, oxyhæmaglobin, alkapton, indol derivative, scatol derivative, phenol derivative, urorubrohæmatin, urofuscohæmatin were all examined for and found to be absent. Hæmatoporphyrin, however, was present, and accounted for the claret-colored urine. The vegetable pigments were absent; the urobilin derivatives were not present in sufficient amount to produce color."

Dr. Carpenter forwarded a specimen to Prof. J. Bergen Ogden, of the Harvard Medical School (whose article on hæmatoporphyrinuria appeared in the *Boston Medical and Surgical Journal* of February 24, 1898), who coincided with him that the pigment was hæmatoporphyrin.

The question suggests itself, Is there a direct relation between acute inflammatory processes of the cord and spinal nerves and the appearance of hæmatoporphyrinuria? Ogden, in the paper referred to, reports a case of post-diphtheritic neuritis which was under the care of Dr. George B. Shattuck and Dr. C. F. Whitington, of the Boston City Hospital, in which there was loss of sensation reaching upward to the waist line, accompanied with involuntary micturition and dejection, and in which hæmatoporphyrinuria was present. In this case also it is possible that the condition was secondary to the taking of trional, which had been given in gramme doses. But there had elapsed a period of eleven days on one occasion between the taking of the drug and the appearance of the pigment in the urine. In my case it is believed that the coloring matter appeared before either trional or sulphonal had been taken, as the urine was observed to be very dark, although not distinctly claret color, more than four weeks before either drug was administered. Two days after taking fifteen grains of sulphonal in divided doses, which were believed to have been vomited, the claret color of the urine attracted attention. On the 9th of September one gramme of sulphonal was given and on the 10th one gramme of trional. She died on the night of the 24th of

September, and the symptoms of hæmatoporphyrinuria were continuous from the 10th to the 24th. It is thus seen that fourteen days elapsed without the administration of the drugs in question, and that only one gramme of each had been taken.

DISCUSSION.

DR. PUTNAM: I was very much interested in Dr. Stockton's case, because I have had one myself of almost precisely the same character. The patient was a man past middle life, who was in a debilitated state of health, partly as the result of chronic disturbance of nutrition and partly from the abuse of morphine, which, however, he was not taking at the time of his last illness. He had been suffering for some months with symptoms apparently those of what might be called multiple neuritis, or Landry's disease, characterized by increasing paralysis, with tenderness of the muscles and great emaciation. He finally died with gradual failure of respiration and heart action, and he also for a week or more before death had this claret-colored urine. In that case also trional and sulphonal had been given, but none had been used for at least thirteen days before his death occurred. The autopsy was made by Dr. Joslin and myself, and the specimens were examined by Dr. Wright, who found no change in the spinal cord, but signs of degenerative neuritis.

DR. JANEWAY: I can add another similar case, that of a lady who had been a nervous woman for a number of years and was taking trional, when she suddenly developed symptoms of nausea and vomiting and such a neuritis as described, with voidance of this claret-colored urine. She has nearly recovered, however, after a period of a year and a little over. She had a mitral insufficiency, which seemed to be organic, but that is all gone, and she is making a good recovery, though slow. I questioned her very closely, and the only agents we could find in connection with the trouble was that she was using trional in from ten to twenty-grain doses at night to produce sleep.

THE RELATIVE INFREQUENCY OF ACUTE SPECIFIC INFECTIONS IN THE FIRST YEAR OF LIFE, WITH A PROBABLE EXPLANATION FOR IT.

By A. C. ABBOTT, M.D.,
of Philadelphia.

My object in speaking upon this topic is less to present anything that is new than to emphasize certain interesting phases of it that I think have not received the attention that their importance warrants.

If the general mortality of a community be tabulated according to certain age-groups we invariably find that the greatest number of deaths fall in the group comprising those individuals under one year of age (see Table I.). If, in a similar manner, we again tabulate the deaths from certain of the commoner *specific infections* we shall now find that in this same group there is a very much smaller number of deaths (see Table II.); and if we further classify the deaths during this first year of life, according to age by months, we find that the great majority fall in the second half of the first year (see Table III.).

This is, of course, familiar to you all; though from the statements encountered in many of the writings upon the influence of age in predisposing to the infections of childhood it is rare that precise data are given in illustration of the varying susceptibilities at different ages during this period of development, and practically never that a reason is offered in explanation of the phenomenon.

I am not sure that it can be explained in a way that will satisfactorily meet all cases, but there are certain facts that have been brought out in the course of purely experimental work that are, I believe, worthy of more serious consideration in this connection than is usually accorded them.

TABLE I.

Showing distribution of deaths from *all causes* during the period of childhood. Arranged according to particular age-groups.

Localities.	Period.	Total number of deaths, all ages, all causes.	Age. Under 1 year. No. of deaths.	Under 1 year. Per ct. total.	1–5 years. No. of deaths.	1–5 years. Per ct. total.	5–10 years. No. of deaths.	5–10 years. Per ct. total.
Boston	6 years, ending May 31, 1890	60,021	14,117	23.5	7,674	12.8	2,051	3.4
New York		250,359	79,022	31.5	38,971	15.6	7,619	3.0
Brooklyn		112,467	35,026	31.1	17,880	15.9	4,637	4.1
Philadelphia		134,878	38,195	28.3	16,409	12.2	4,328	3.2
Baltimore		56,052	18,790	33.6	7,406	13.2	1,630	2.9
Dist. Columbia		32,515	10,450	32.3	3,568	10.9	1,059	3.2
All England	1893–97 inclus.	2,705,991	693,555	25.6	346,714	12.8	75,220	2.8

TABLE II.

Showing distribution of deaths from three specific infections common to children. Arranged with regard to particular age-groups in the period of childhood.

Localities.	Period.	Diseases.	Total number of deaths all ages.	Age. Under 1 year. No. of deaths.	Under 1 year. Pr. ct. total.	1–5 years. No. of deaths.	1–5 years. Pr. ct. total.	5–10 years. No. of deaths.	5–10 years. Pr. ct. total.
Boston	6 years, ending May 31, 1890	Measles	6,414	1,760	27.4	4,154	64.8	373	5.8
New York									
Brooklyn		Scarlet fever	8,969	585	6.5	5,732	63.9	1,982	22.1
Philadelphia									
Baltimore									
Dist. Columbia		Diphtheria	22,238	1,515	6.8	14,148	63.6	5,192	23.1
All England	1893–97 inclus.	Measles	64,687	14,795	22.8	45,459	68.8	3,761	5.8
		Scarlet fever	26,599	1,561	5.8	15,412	58.0	6,705	25.2
		Diphtheria	50,949	3,371	6.6	29,378	57.6	13,343	26.2

TABLE III.

Showing distribution of deaths from three specific infections during the first year of life. (From Annual Reports of Registrar-General of Great Britain, 1893–97 inclusive.)

Diseases.	Total number of deaths among children one year old.	Age.					
		0–3 months.		3–6 months.		6–12 months.	
		No. of deaths.	Per ct. total.	No. of deaths.	Per ct. total.	No. of deaths.	Per ct. total.
Measles	14,795	395	2.7	1,161	7.7	13,257	89.6
Scarlet fever	1,561	118	7.6	192	12.3	1,251	80.1
Diphtheria and croup . .	3,371	279	8.3	450	13.3	2,642	78.4
... ...	... ...	... ...	... ...	... ...	... ...	... ...	... ...
Distribution of deaths from *all other* causes among the same age-groups:							
Other causes . . .	673,810	335,549	49.8	144,274	21.4	193,987	28.8

On the first thought one might be tempted to say that during the early months of life exposure is less, and that, therefore, the opportunities for infection are fewer than at a later period, and in many cases this is doubtless true; but I question if this is sufficiently constant to serve as a trustworthy generalization on this remarkable phenomenon; for certainly among the poor and destitute—no inconsiderable part of every large community—where the care of the infant usually falls to an elder child during most of the time that the baby is not actually nursing, there are opportunities in abundance for its infection.

I believe the explanation lies in another direction, and that exposure or non-exposure to infection has little or nothing to do with the comparative immunity from the commoner specific diseases that is enjoyed by infants during the better part of the first year of life.

There are two hypotheses that appear to bear on the subject. One of these is the doctrine advanced by Baumgarten in connection with the latency of tuberculosis in the new-born. Briefly stated, his idea is that in the new-born the bacillus of tuberculosis, if present, is prevented from developing and exhibiting its pathogenic functions through the antagonism of the actively developing tissues of the child. Whether this idea is applicable to other infective micro-organisms

that gain access to the tissues of the child or not it is impossible to say. Indeed, with regard to tuberculosis, on which the hypothesis was designed to bear in particular, Baumgarten's idea has not met with universal acceptation.

The next hypothesis, and the one that appeals more favorably to me, is that which comprehends the results of Ehrlich's investigations on the hereditary transmission of immunity.[1] Without entering into the details of the investigations which led to it, it will suffice to say that Ehrlich demonstrated that if a female animal (a mouse) be artificially immunized against certain vegetable poisons, that she transfers to the young by way of the milk during the nursing period a something that protects her offspring from intoxication by the same poison so long as they are sucklings. The "passive" immunity conferred to the offspring in this way is not permanent. Ehrlich found that it was fully operative up to about six weeks after birth, when it gradually became less evident, and by the fourth month had entirely disappeared. The question that naturally arises is: Can these observations be used in explanation of the comparative rarity of specific infective processes in the first year of life among human beings as noted above? In his communication Ehrlich expresses himself in the affirmative on this subject.

If we will recall the fact that a large proportion of adult human beings have passed through some or all of the acute specific infections during the period of childhood or youth, and if we further recall the fact that in the majority of instances recovery from such attacks confers more or less *permanent* immunity to the individual, it does not seem unreasonable to believe, in the light of Ehrlich's work, that a mother who has acquired a lasting "active" immunity in this way, may during the period of nursing—that is, during something more than half of the first twelve months of life of her child—convey to that child through her milk an agent that protects it temporarily against the same disease from which she herself had in her youth recovered, and that with the cessation of nursing this protection is withdrawn. Whether this is or is not the true explanation of the phenomenon, it appeals to me as certainly the most satisfactory scientific interpretation that the subject has received.

[1] Ehrlich. Zeitschrift für Hygiene, 1892, B. xii., S. 183.

DISCUSSION.

DR. GEORGE B. SHATTUCK: I should like to question the theory so far as diphtheria is concerned. The proportion of people who have had this disease is comparatively small, the immunity conferred is comparatively slight and brief, so that it seems to me diphtheria on that list stands on a different footing from measles and scarlet fever, and must probably have a different explanation.

RECURRENT VOMITING IN CHILDREN.
(CYCLIC VOMITING.)

By J. P. CROZER GRIFFITH, M.D.,
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THE following case-histories illustrate a condition which seems well worthy of a more extended consideration than has been devoted to it hitherto. The first case is an instance of the disease in a mild form, and, in a way, on the border line. The second is one of unusual severity and shows how severe the disease may become. The third and fourth go still further, since both the children died.

CASE I.—Marcellus H., born January 5, 1895. In infancy his digestion was always feeble, and, although many ways of feeding were tried, vomiting frequently occurred. His general condition was, however, pretty good until July, 1895, when appetite failed and indigestion increased. This latter was frequent through the winter of 1895–96, apparently the direct result of experimenting with various foods. Later he improved in health and in power of digestion, although he was not robust. Vomiting ceased to be a symptom of any moment. With the onset of warm weather in 1896 he commenced to have irregular fever, which lasted through most of the summer. Again, in 1897, as warm weather approached, he suffered from fever which continued nearly the entire summer, during which time he was under my care. This fever seemed to be due to chronic auto-intoxication of intestinal origin, although there were very few distinct evidences of indigestion. During the winter of 1897–98 he was in fair health. In the summer of 1898 he again had more or less continued fever, the symptoms being very similar to those of the preceding year, although the temperature was not so high. Vomiting was unusual and occurred only with other evidences of indigestion. The bowels were loose at times. In September, 1898, he began to improve in health and the fever ceased.

Up to this period in his life the occasional vomiting had been apparently clearly the result of acute indigestion. Now, however, he began to have certain severe attacks of vomiting of the type presently to be described, which seemed entirely unassociated with any indiscretion in diet or symptoms of

indigestion. These attacks occurred about every three or three and a half weeks with some degree of regularity, and continued to appear until early in the spring of 1899, when he again came under my care. I saw him in March, 1899, at the beginning of one of them. Since that time he has had but one attack, and that a slight one. The nature of an attack was much as follows: The child would be apparently well and lively for some weeks. Then, without any indiscretion in diet or other discoverable cause, or any decided symptoms of indigestion, he would lose his appetite for a few days and become constipated. High fever then developed, and with this vomiting quickly began. The latter lasted during one or two days, and occurred frequently, especially if food or anything else was put into the stomach. Fever abated after vomiting began. There was decided prostration, restlessness, rapid respiration, much thirst, and retracted abdomen. Complete loss of appetite continued. Loss of flesh seemed rapid. Constipation was present during the attack, but could be overcome by purgatives, although with some difficulty. Relief of the constipation obtained in this way was sometimes accompanied by relief of the vomiting; but in other attacks, where no purgatives or enemata were given, vomiting ceased before the bowels were opened. There was, in fact, no clear connection between the relief of the constipation and the cessation of the vomiting. The urine was sometimes diminished in amount before the attack, and during it it remained scanty. The urine obtained on March 18th, when the child was beginning to convalesce from the attack in which I saw him, contained a large deposit of crystals of uric acid. Analysis made by Prof. John Marshall, of the University of Pennsylvania, gave a ratio of uric acid to urea of 1 : 116. A specimen passed on May 26th, at a time when the child was in excellent health, still showed a diminished excretion of uric acid. Convalescence from the attacks was rapid. The early evacuation of the bowels, an almost total withdrawal of food, and the administration of small doses of bromide salt with a febrifuge, appeared to abbreviate the attacks.

CASE II.—Henry A., born May 12, 1891. He had always been a nervous child, but had had good general health. His first attack of recurrent vomiting took place in July, 1894. After this he had attacks in January and December, 1895. These earlier seizures lasted about one day, not often longer. Constipation was not noticed, if present. The vomiting was severe, but not alarming. It did not appear to be connected in any way with the diet, and was unattended by any evidence of indigestion. There was always restlessness and sighing respiration. The attack was always attended by tonsillitis. Recovery was rapid, unless tonsillitis had been severe. The first truly alarming attack, which was nearly fatal, took place in March, 1897. He had another seizure in January, 1898, and again in May, 1898, but in neither case severe. A second severe attack occurred in July, 1898. There has been no recurrence.

The two severe attacks must be described somewhat in detail. The first commenced about March 31st with severe vomiting. Very soon this symp-

tom became grave. It was almost continuous, everything which went into the stomach being promptly ejected, and efforts at vomiting occurring frequently, even though nothing was taken. The bowels had been obstinately constipated, in spite of purgatives and of large enemata frequently given, and the attending physician feared intestinal obstruction. I saw the boy late on April 2d. On this date for the first time a bowel movement had been obtained, yet without relief of the gastric condition. Prostration was extreme; there was great restlessness and much thirst. The respiration was accelerated and sighing, especially when he was asleep. The child slept only fitfully and after an attack of vomiting, soon rousing, tossing, and suffering another attack. There was no pain, tenderness, or retraction of the abdomen. The secretion of urine was diminished. All treatment had been unavailing, including the administration of chloral and bromides by the bowel, and the prognosis seemed most grave. I advised the giving of morphine by hypodermatic injection. I did not see the child again in this attack, but learned the following details later: Owing to a fear of the drug on the part of the attending physician the morphine was not given. Vomiting continued, and the exhaustion increased until finally the child lay helpless on his side, while every few moments a little dark or blood-stained fluid ran from his mouth, forceful vomiting being no longer possible. Constipation was now absolute. Another consultant was called, and various drugs were administered by the mouth, but without any change for the better being effected. At last, after several more days had elapsed, with the death of the child apparently certain and not far distant, the attending physician in desperation began narcotizing him with morphine in the way suggested. The good effect was immediate, the vomiting ceasing at once and permanently. The morphine was continued for a short time. Within twenty-four hours the bowels were opened by enema, and an uneventful convalescence was established.

In the attack of June, 1898, the child had been ill for one or two days before I saw him. Very little urine had been voided, and constipation had been absolute. There was no great prostration. The attending physician had wisely refrained entirely from efforts to feed him by the mouth, and the bowel had been used for nutrient enemata only, without any effort to produce a stool. Apparently as a result of this conservative treatment, the vomiting was already better when I arrived. There had been no abdominal pain, tenderness or retraction. I continued nutrient enemata, and gave Rochelle salts in small repeated doses by the mouth. Vomiting did not occur, and in about twelve hours sighing respiration and restlessness ceased, the bowels were freely opened, and appetite returned. Convalescence was rapid.

The vomited matter in this case was never especially sour. There was never any peculiar odor to the breath. The amount of urine was generally diminished before an attack, and sometimes very greatly so. This scanty secretion continued during the attack. No albumin was found at any time.

The parents, who are most intelligent and observing, have not been able in any of the attacks to see that evacuation of the bowels by purgatives or

enemata caused, or was even followed by, cessation of the vomiting. On the other hand, they have found that the chief or only premonitory symptoms were a congestion of the head and a decided tendency to suppression of urine; and it has appeared to them that an attack could be prevented, when these symptoms developed, by prompt drainage of the system through the bowel, the flushing of the kidneys by large draughts of water, and the withdrawal of all food except milk.

For the notes of the following case I am largely indebted to Dr. Alexander Marcy, Jr., the attending physician. I saw the boy in one of the attacks occurring in the spring of 1896.

CASE III.—A. H., born August, 1891. He was a healthy child until the age of two years, except for the occurrence of gastro-enteritis with meningitic symptoms at fourteen months. In June, 1893, he had his first attack of recurrent vomiting, which lasted only a few days and was supposed at the time to be an ordinary indigestion. A second severer attack occurred in February, 1894, and another slight one in July, 1894. There were no others until February, 1896, when a much more severe one took place. Two seizures occurred in March, 1896, and in May one which lasted eight days, and was so severe that recovery seemed doubtful. In July, 1896, he had a seizure which lasted ten days, in which his life was despaired of, and from which recovery was slow. The final attack occurred in October, 1896. It lasted but two days and terminated fatally.

The symptoms in all the attacks but the last were much the same. After some loss of appetite, coating of tongue and malaise during the day, vomiting came on suddenly, generally at night. This soon became obstinate and frequent, occurring every few minutes, the vomited matter being at first the ingested food, and later mucus and bile, sometimes with streaks of blood. There was great restlessness, continued tossing, and but little sleep. The pulse grew rapid and weak, and respiration irregular and sighing. The temperature was always elevated on the first day. After this it sometimes fell below normal, to rise to fever heat later; sometimes it continued elevated throughout the attack. Normal stools occurred at first, either spontaneously or by enema. Later, after twenty-four to forty-eight hours, the bowels were obstinately constipated, and peristalsis seemed to be arrested. When the attack was over the bowels would move of themselves. Abdominal pain was always present, but was of slight degree. Thirst was intense. The breath had often a peculiar odor. The urine was apparently increased in amount at first, acid, and of high specific gravity, but after one or two days it became scanty, and later even almost suppressed. Indican was present in considerable quantities at first; later acetone appeared. Albumin was absent. Exhaustion finally became extreme, the eyes sunken, and the whole body shrunken, dry, and cold. The mind was always unaffected. Gradually the vomiting became less frequent, restlessness diminished, and recovery began

and advanced, usually with rapidity, but slowly after the severest attacks. During convalescence there was often considerable general pruritus.

The last attack differed somewhat from the others. Vomiting was less frequent but unusually violent, and in a few hours the child was vomiting blood. In twenty-four hours a nephritis had developed, with albumin, casts, and blood in the urine. Death followed from cardiac failure.

As regards treatment, hypodermatic injections of morphia or the administration of chloral and bromides appeared to be of slight service in some attacks, but generally were of no avail.

The following case likewise occurred in the practice of Dr. Marcy. I saw the child in one of the attacks and on a number of other occasions, both when well and when seizures seemed to be threatening.

CASE IV. Honoria H., born March 2, 1892. She had been a healthy child up to the age of about three years, when she began to have attacks of vomiting, which developed suddenly, were attended by fever, lasted a short time, and were supposed to be due to indigestion. In September, 1895, she had a very severe seizure, lasting a week and much worse than any which had preceded. Exhaustion at this time was so great that recovery was despaired of. There was no return of the trouble until July, 1897, and again in August, 1897, when she had the worst attack yet experienced, which lasted eight days, during most of which time death was momentarily expected. I saw her for the first time on October 1, 1897, when she was apparently well. After this, during the early part of October, she appeared often to be on the brink of an attack, suffering from anorexia and coated tongue, and being very languid. None occurred, however, and the child's general health became good until February 21, 1898. On this date, after about a week of premonitory symptoms, vomiting began, and continued nearly constantly for twenty-four hours. It then lessened somewhat, but soon returned in force. I saw her about the 26th, and found her exhausted and with vomiting still very frequent, although apparently lessening. A few days later she was seen by a prominent surgeon of Philadelphia, who inclined to the diagnosis of appendicitis, but believed that operation was not justifiable, as recovery seemed impossible. She did, however, recover. About a week after convalescence she suffered for a time from diffuse severe articular pains, later changing into mere stiffness, but unattended at any time by swelling of the joints. She was later, when in good health, re-examined by the surgeon, who diagnosed chronic appendicitis, and urged operation. The appendix was removed in April, 1898. Macroscopical examination showed no material change. Microscopically there were evidences of inflammatory alterations. After the operation the child continued to improve in health, and it was at first thought that this depended in part or wholly upon the removal of the appendix. But in March, 1899, she had another attack of vomiting, worse than any previous one, and she died exhausted after an illness of nine days.

Autopsy showed necrotic changes in the mucous membrane of the stomach and intestines, slight parenchymatous alterations in the pancreas, spleen and kidneys and fatty infiltration of the liver.

The symptoms in this case were in most respects identical with those described in Case III. There were the same uncontrollable, frequent vomiting, loss of appetite, restlessness, sighing respiration, rapid pulse, and inconsiderable abdominal pain and tenderness. The secretion of urine was affected in the same manner, indican and acetone being present as in that case. In contrast, however, although the onset was sudden in some attacks, in others the prodromal symptoms lasted longer, coated tongue, loss of appetite, and restlessness continuing for several days. Pruritus during the attack was more marked. Toward the end of the last and fatal attack albumin and casts appeared in the urine.

Repeated examinations of the urine were made for me by Professor John Marshall, but the results were only partially satisfactory, owing to the inability to control the case and the difficulty in procuring sufficient urine for analysis. Examination on October 16, 1897, when the child exhibited what appeared to be prodromal symptoms, but which, however, did not advance further, showed neither indican nor acetone. On December 2, 1897, the child being at this time in good, general health, the uric acid urea ratio equalled 1 : 113. No indican or acetone was present. On February 22, the second day of an attack, the uric acid urea ratio was 1 : 176. Acetone and indican were present.

In the way of treatment, morphine hypodermatically or the giving of the bromides and chloral seemed at times to do some good, but were not to be depended on.

Very little definite appears in medical literature concerning this curious disease, although in my reading of it I have doubtless overlooked much. The Paris Thesis by Solelis was not accessible to me. Most writers refer to the article by Leyden as the first upon the subject. This author (*Zeitsch. f. klin. Med.*, 1882, iv., 605) discusses certain gastric crises under the title of "periodical vomiting," which condition he regards as a pure neurosis, the symptoms of which are practically identical in every way with those of the gastric crises of tabes. In the cases he described there were present great abdominal pain, frequent and very profuse vomiting, constipation, scanty urine, retracted abdomen, great exhaustion, and no fever. The abdominal pain was a very prominent symptom, and was sometimes associated with other neuralgias. There was no regularity in the intervals between the attacks. All the cases detailed occurred in adults. Meyerhoff (*Deutsche med. Wochen-*

schrift, 1881, vii., 710) describes in detail a similar case in a woman, in which abdominal tenderness and severe pain always attended the vomiting. Meisl (*Centralblatt f. d. gesammte Therapie*, 1897, xv., 459) reports cases very similar to those of Leyden. He states, however, that there was no pain except during the act of vomiting, and he insists on the regularity of the recurrence of the seizures. This regularity, at variance with Leyden's experience, is also insisted on by Einhorn (*Twentieth Century Practice of Medicine*, vii., 343) in an article on the subject. Rémond (*Arch. gén. de Med.*, 1889, clxiv., 38) collects from medical literature and from his own experience cases of periodical vomiting. In all of these intense pain was the most prominent feature. All were in adults.

There are a few other writers referring to the condition described by Leyden, but nearly all of them dwell upon the elements of marked abdominal pain as almost or quite pathognomonic, and compare the attacks to the gastric crises of tabes. The condition appears to be an undoubted neurosis, which, although allied to is yet different in some important respects from that which my own cases illustrate, about the purely neurotic nature of which there is some doubt. The difference in the amount of pain is one great characteristic. This view is held, too, by Boas (*Deutsche med. Woch.*, 1889, xv., 864), who, in describing a series of cases of gastric neuroses, draws a sharp distinction between gastric crises and periodical vomiting, basing this on the marked element of pain and the presence of an excess of HCl in the secretion in the former, and the slight development or absence of pain and the absence of an excess of HCl in the latter. He agrees, however, with those who insist upon regularity in the periodicity of the attacks of vomiting. The cases of all the writers mentioned occurred in adults.

We have next to consider another condition described in medical literature, which also appears to differ from that now under consideration. Langford Symes (*Dublin Journal of Medical Science*, 1897, civ., 112) writes of what he denominates "gastric attacks." These occur in children only. There develops suddenly profound nervous disturbances, and the child seems alarmingly ill. There are constipation, vomiting, and even collapse. But the affection always depends on definite demonstrable dietetic causes, and the vomiting often relieves the attack. W. Saltau Fenwick (*Disorders of*

Digestion in Infancy and Childhood, 1897, 233) describes under the title of "Recurrent Gastric Catarrh" a condition which, he states, is identical with "periodic" or "cyclic" vomiting. He claims that it is extremely common, generally mild, and depends upon a catarrhal state of the stomach. All this is at variance with the experience of other clinicians; and we are forced to the conclusion that the great majority of the cases on which his views are based do not belong to the category now under consideration.

A number of writers have described the disease as my own cases represent it. Gee (*St. Bartholomew's Hospital Reports*, 1882, xviii., 1) details nine cases of what he denominates "fitful" or "recurrent" vomiting, of which probably five certainly belong to the disease now being discussed. Pepper (*Cyclopædia of the Diseases of Children* (Keating), iii., 22; also supplemental volume, 631) contributes a valuable article upon the subject, although without details of cases. Snow (*Transactions of the American Pediatric Society*, 1893, v., 185) gives the details of a case in a girl, aged eight years, which must certainly be classified with my own. In the discussion of this paper, Seibert, Caillé, and Forchheimer reported having seen cases in children. Rotch (*Pediatrics*, 841) gives a clear description, with the details of three cases of eight months, twenty-two months, and nine years respectively. Rachford (*American Text-book of the Diseases of Children*, second edition, 96; *Archives of Pediatrics*, 1898, xv., 605) describes three cases seen by him which are clearly instances of this disorder. The ages were eighteen months, two years, and four years. He makes some important suggestions regarding the pathology of the affection. Holt (*Diseases of Infancy and Childhood*, 287) contributes a valuable chapter upon the disease, with the report of a case in a child of six years, and discusses the relationship of the affection to certain urinary changes. Whitney (*Archives of Pediatrics*, 1898, xv., 839) describes a very typical case in a girl, aged eight and a half years. Marcy (*International Clinics*, ninth series, iii.) gives a graphic description of the affection in three cases, two of which are included in my own report, since they were likewise more or less under my own care. The other case occurred in a girl of six years.

Fuller details of the cases of these writers will be given in the analysis which follows.

SYMPTOMATOLOGY. The four cases which I have observed have a striking likeness to each other, although differing in certain particulars. The first was a mild case, resembling in some respects the condition described by Symes, yet differing in the absence of any discoverable dietetic or other cause. The second case was one of unusual severity ; the third and fourth cases were fatal. Comparing them with the last group of cases to which I have referred as found in literature, we observe a complex of symptoms which is eminently striking and characteristic, and which must be studied more in detail. These symptoms appear in separate attacks, which develop with more or less suddenness, and which are separated by more or less irregular intervals, during which time the child is, as a rule, in excellent health.

Prodromal symptoms of an attack may be absent, and the child begin to vomit without any evidence of previous illness. In other cases there are prodromes, but these are generally insignificant and indefinite, consisting of malaise, some coating of the tongue, loss of appetite, possibly headache, and some disturbance of the bowels, generally constipation, sometimes slight diarrhœa. These last from a few hours to a day, rarely longer. In one of my cases (IV.) prodromes lasted on one occasion a week, and a furred tongue continuing a week was seen in one of Gee's cases. There is, however, never any distinct evidence or history of decided indigestion preceding or in any way connected with the outbreak of an attack.

Vomiting is the first and most striking symptom of the attack itself. From the outset it is obstinate and oft-repeated. At first the contents of the stomach are ejected, not, as a rule, showing any evidence of abnormal fermentation. Later the vomited matter consists of watery fluid, with mucus or bile, and sometimes with blood. Sometimes there is also violent, unproductive retching. Generally everything put into the stomach is promptly vomited. Snow found that in his case the vomited matter contained an excess of HCl, but other writers have not corroborated this. Further investigation is needed on this point. The vomiting may sometimes cease temporarily and then recommence. Generally it continues very frequent until toward the close of the attack and then gradually or suddenly ceases.

Constipation is a very constant but not necessary symptom. It

is sometimes so obstinate that no treatment has any effect whatever, the action of the bowel seeming to be paralyzed. In some cases, however, as, for instance, in that of Snow, it can be readily relieved, although the vomiting continues. In Whitney's case the bowels were slightly loose and offensive. In two of Gee's cases the bowels were not affected, except that they were sometimes whitish in color in one instance. In three of my own cases, although there were sometimes a few loose movements at the very first, obstinate constipation soon became a very prominent feature. In no case reported does it appear, however, that relief of the constipation had any influence in bringing the vomiting to a close. Rather the bowels appear to act because the attack was nearly over. This is also the opinion expressed by Leyden regarding the cases of periodical vomiting reported by him.

The *appearance of the abdomen* does not seem to be uniform. Retraction or flatness is probably common. It is referred to by several writers, and was present in at least two of my own cases. It does not appear to be any greater, however, than would occur in any asthenic state with empty intestines. This is in marked contrast to the periodical vomiting of Leyden. Distention of the abdomen by gas does not seem to occur.

Abdominal pain is a symptom almost entirely absent in the cases which appear to belong strictly to this category. As has been already pointed out, this is in sharp contradistinction to the very marked pain which characterizes both the gastric crises of tabes and the similar idiopathic gastric crises which the cases of Leyden and several other writers quoted represent. There is sometimes slight pain and tenderness during the attack, but no more than the fatigue of the muscles by the constant vomiting can well account for. This absence of severe pain seems to be the common experience of observers of recurrent vomiting in children. Only in one of Gee's cases could pain be called decided.

Thirst is commonly intense, due doubtless to the abstraction of liquid from the system and the inability to retain any ingested.

Appetite is generally completely lost. The *tongue* is variable. It is not, as a rule, as greatly coated as in cases of indigestion. Rotch refers to this fact as of diagnostic importance. The tongue was dry in Holt's case, and slightly coated in Snow's and Whitney's cases.

In two of my own cases (III. and IV.) it was at first slightly coated, and later more so. Case I. also exhibited a coated tongue. I have no record of its condition in Case II. The *breath* is described as of a sickening odor by Rachford, while in two of my cases, Dr. Marcy, who was in attendance, noticed a very peculiar odor (acetone ?). In the other two cases nothing characteristic was observed. Other writers do not refer to the matter. *Sore throat* always attended in one of Gee's cases ; tonsillitis occurred in one of the attacks in Snow's cases, and in some of the earlier attacks in one of my own (II.).

There appears to be no rule about the *temperature.* Rotch describes it as normal or subnormal in his cases. In the case reported by Holt it was elevated at the beginning, and later subfebrile or normal. In Whitney's case there was slight fever. In Snow's the temperature ranged from 100° to 105° F. In Seibert's case there was fever, as there was also in Rachford's cases and in some of Gee's. In my own experience there was decided fever in Cases I., III., and IV. ; no record in Case II. It would appear, then, that in recurrent vomiting there is apt to be more or less fever during the attack, although this is not a necessary symptom.

Respiration is decidedly affected. In my second and third cases it was peculiarly sighing ; in the fourth case irregular, and in the first case rapid. In Rachford's cases it was rapid, and often very greatly so as the exhaustion increased. The *pulse* generally becomes rapid. Often it is slightly irregular. The only exception I have noted to this opinion is the statement of Rotch, that the pulse is sometimes slow.

The condition of the *urine* is of great interest, but as yet no conclusions can be drawn regarding it. Rachford describes the urine as scanty during the attack, and in one case containing albumin and casts, which disappeared at once when the attack was over. The only case carefully studied with regard to the amounts of urea and uric acid present has been that of Holt. In this the ratio of uric acid to urea before the attack was 1 : 54 ; during the attack, 1 : 157 and 1 : 132 ; during convalescence, 1 : 50. In my own cases circumstances prevented the more extended and exact study of the urine which might have thrown light upon the pathology of the disease. In Case I. the secretion of urine was sometimes increased

as a prodromal symptom, but scanty during the attack. The analysis during convalescence, made for me by Professor John Marshall, showed a ratio of uric acid to urea of 1 : 116. It must be stated, however, that some trace of the symptoms was still remaining. In Case II. the amount of urine was generally diminished, and sometimes greatly so, during the prodromal period and in the attack itself. During convalescence urine was passed freely. In Case III. urine was increased in amount just before the attack, and contained indican. Later it was diminished and acetone was present. In the last attack it contained albumin and casts. In Case IV. exactly the same condition was observed as in Case III. Besides this, an examination for uric acid and urea at a time when the child seemed in good health gave a ration of 1 : 113. Another examination, made on the second day of an attack, gave a ratio of 1 : 176. The observations on the uric acid urea ratio in my own cases are, therefore, not conclusive.

The *nervous and general symptoms* are interesting. In Snow's case convulsions commonly occurred in the earlier attacks, but were absent in later ones. I find no other instance of this symptom recorded. Extreme restlessness with constant tossing and the occurrence of very little sleep were noticed in two of my cases (III. and IV.). The presence of restlessness was observed by Rotch in one of his cases. Later in the disease exhaustion becomes extreme, emaciation is marked, and the child lies apathetic, although generally entirely conscious. In bad cases a state of collapse is present, from which it may seem impossible that the patient can rally. Itching of the skin was present in two of my cases.

The *duration* of the attacks is very variable. Recovery is generally very rapid. In Holt's detailed case the attack lasted always five days, although improvement began on the third day. In Whitney's case it lasted about three days, and convalescence was rapid. Rotch regards two to three days as the average duration, and the recovery sudden; but in some of his cases the attacks lasted seven days, and in one instance two weeks, with slow convalescence. The attacks in Snow's patient varied from five to sixteen days in length, and in Rachford's patient from two to four days. In one of Gee's cases the duration was about ten hours, in another seven to ten days, in another eleven days.

In one of my own cases (II.) the worst attack lasted possibly a week. In another case (III.) the longest was ten days, but the final fatal attack only two days.

Even in the cases in which exhaustion has been extreme and vomiting incessant, convalescence is generally astonishingly rapid. The first sign of improvement is perhaps a diminution in the frequency of the vomiting, with return of some strength to the pulse and some warmth to the extremities, while the whole appearance changes for the better. Then vomiting soon ceases entirely, appetite returns, and the child is practically well except for a certain degree of weakness, which also rapidly disappears.

The *frequency* of occurrence of attacks varies greatly. In the disease described by Leyden the seizures came on at irregular intervals. Certain other writers, however, as has already been pointed out, have insisted on a decided regularity in the occurrence. In the recurrent vomiting which we have under consideration, on the other hand, no case reported has exhibited any tendency to distinct periodicity except Whitney's patient. In this case the intervals were generally three months. Holt's patient usually went five to six months without an attack, and Snow's from six to twenty-five weeks. In Rachford's cases the intervals varied from four to eight weeks. So, also, in my own cases no regularity at all could be discovered. In Case I. the attacks occurred every few weeks during a few months, with no attacks since. In Case II. the intervals varied from two to fifteen months, with seven attacks in all; in Case III. from one to seventeen months, with eight attacks in all; in Case IV. from one to twenty-two months, with five attacks in all.

Nature and Cause. To the group of cases under consideration we can perhaps best apply the term "recurrent vomiting"—a name first employed by Gee. The title "cyclic," although popular, is misleading, because a cycle denotes a definite regularity in occurrence. "Periodical" likewise implies a certain degree of regularity. "Persistent vomiting," as it is called by Rotch, does not indicate that the attacks recur. There seems to be no term left us, then, but that of "recurrent vomiting."

This group of cases seems certainly different in nature from that which the cases described by Leyden, Rémond and others form, in

which pain is such a prominent feature, and of which the purely neurotic nature seems assured. It differs, too, from the affection described by Fenwick, Symes, and in part by Gee, in which dietetic errors are apparently the certain immediate cause. Yet even in recurrent vomiting, as I have limited the term, the cause and nature are very possibly not the same for all cases. It seems at least sure that the attacks depend in no way upon errors in diet. As the case-histories show, there is comparatively perfect health between the attacks, so far as the digestive apparatus is concerned. It is true that the prodromal symptoms are to some extent those of disturbed digestion, but they develop in spite of the greatest care in the diet, and seem to come from inside the patient rather than from without. Moreover, when the attack has commenced the emptying of the stomach by vomiting gives no relief, as would be the case in ordinary acute gastric disturbances.

The points in common shared by recurrent vomiting, the painful periodic vomiting of adults, and the attacks of gastric pain with or without vomiting, which occur in tabes, suggest the view that recurrent vomiting may be a gastric neurosis. That this is the true nature is the view of Rotch and of Whitney. Snow believes this to be true of his case, and regards the marked hyperchlorhydria of the vomited matter as confirmatory of this view. But, as previously stated, it is not proven nor even likely that hyperchlorhydria is the general condition. There is, indeed, decided ground for the belief that the recurrent vomiting of children is not a pure gastric neurosis, as the periodical vomiting of Leyden is claimed to be. Rachford makes the valuable suggestion that the attacks are due to lithæmia or some condition allied to it, and believes that there is the absorption and storing up in the system of some leucomaïnes. He considers the disease a lithæmic gastroneurosis allied to migraine. This view is supported by the fact that in one of his patients the symptoms changed into those of migraine as the child grew older. The condition of the urine in Holt's case points in the same direction. Yet further study is needed. The examinations of the urine in two of my own cases are not entirely confirmatory. The occurrence of albumin and tube-casts in one of Rachford's cases, and of a terminal nephritis in two of my own, together with the post-mortem findings in one of them, certainly suggest that the disease is due to the pres-

ence of some toxic substance circulating in the blood—probably not uric acid, but some toxalbumin possibly allied to it. The presence of pruritus in two of my cases and the occurrence in one of them of diffuse articular pains after an attack point toward a disordered hæmic state. There very probably occurs a gradual storing up in the blood of some toxic substance, possibly developing primarily in the intestine, possibly formed in the tissues, until finally the limit of tolerance is reached and an attack takes place. This is the view likewise to which Pepper clearly leans.

The presence of acetone in the urine in the worst attacks of two of my own cases probably indicates that great disturbances of metabolism are present, and is a further proof of the existence of a toxæmia. Acetone itself, however, cannot be considered the poison which produces recurrent vomiting, since the symptoms of acetonæmia are not such as these cases exhibit.

We may naturally conclude, then, that recurrent vomiting may perhaps be a neurosis, but, if so, is one of toxic origin, in some way connected with faulty metabolism.

Regarding the influence of *age*, the disease may begin at any time in childhood, but in the majority of cases the first attacks were seen within the first three years of life, although generally after the first year.

The existence of a *neurotic* family *history* has been observed in a number of instances, and may well be a predisposing cause. In Rachford's cases a gouty family history is reported. Sometimes the child itself is distinctly neurotic and high-strung, as in the case of Whitney and in one of my own (II.). Occasionally, too, it has been reported that the children have been of rather delicate health. But in the majority of instances the general health has been excellent.

There may possibly be various immediate determining causes for an attack other than those mentioned. Exhaustion, fatigue, exposure to cold, and over-excitement have all been referred to in a general way by writers. But the actual association of these with attacks is most uncertain if we study the details of published cases. The most careful supervision of the life of my own cases failed to show the influence of these or any other immediately exciting causes.

Diagnosis. The diagnosis is not difficult when the attack is well established and is not the first from which the patient has suf-

fered. As already pointed out, recurrent vomiting is to be distinguished from the periodical vomiting described by Leyden. This latter affected adults, was always unattended by fever, and exhibited abdominal pain as a very prominent and often the most prominent symptom. The onset of some acute infectious disease can generally be distinguished by the development of other symptoms which are characteristic. Meningitis, particularly the tubercular form, may cause confusion at first. But the onset is much more gradual in the latter affection, vomiting is not commonly so frequent, and there is an increasing apathy and tendency to stupor, with rigidity, and finally with vasomotor and possibly ocular symptoms, all of which are quite distinctive. Nephritis is to be distinguished by a careful study of the urine at the onset. Acute indigestion is differentiated by the initial heavily-coated tongue and other signs of a disturbed stomach, the character of the vomited matter at the beginning, the tendency for diarrhœa to develop soon in most cases, and the relief which vomiting usually gives after a few hours or a day have elapsed. Especially characteristic of recurrent vomiting is the tendency to repeated attacks which can in no way be associated with the ingestion of unsuitable food. Intussusception or other form of intestinal obstruction causes, perhaps, the greatest difficulty in diagnosis, especially as obstinate constipation is such a prominent symptom of recurrent vomiting in many cases. In one of my own patients (II.) obstruction was strongly suspected by the physician in attendance. Only a careful study of the case will enable a decision to be made, and then not always with certainty. Chief among the points of diagnosis in favor of recurrent vomiting is the tendency to repeated attacks, and the absence of severe abdominal pain. As contrasted with intussusception there is also the absence of bloody mucous stools and of any discoverable tumor. Generally, too, although constipation can be temporarily relieved by treatment, the vomiting persists until the attack is about to terminate.

PROGNOSIS. This is generally good, although not necessarily so. Recovery nearly always takes place, even from a condition of most alarming prostration. That cases do die, however, two of those reported show.

With regard to the likelihood of the recurrence of attacks, experience with the disease has not been sufficient as yet to allow of any

positive conclusions being formed. It seems probable, however, that the disposition of the attacks to recur diminishes as the child grows older. This we can reasonably hope for, since we know that in children vomiting is brought on by many causes much more easily than in later life. In one of my own cases (I.) the affection seems to have disappeared. In another (II.) a longer time has now elapsed than ever occurred before. In one of Rachford's cases the disease was replaced by migraine as the child grew older. In Holt's case and in one of Rotch's the disease seemed to cease with increasing age.

TREATMENT. This is most unsatisfactory. The attack once developed generally goes on in spite of treatment until it exhausts itself. Being entirely ignorant of the nature of the exciting or more remote causes, our preventive treatment can be only experimental. Every element which can be even suspected as an etiological factor must be sought for and removed. Alterations in the diet should be tried; overwork and overplay guarded against, and constipation most carefully prevented. If prodromal symptoms seem threatening, a free purgative may possibly do good by removing poisonous matters from the blood. Care must constantly be taken to maintain a free action of the kidneys.

Should an attack have actually commenced the first indication is to open the bowels freely by an injection, or, still better, by saline cathartics or calomel if the child can retain them. But after the first effort it is well to administer nothing whatever by the mouth, whether food or medicine, thus giving the stomach absolute rest. The use of opening enemata should be discontinued, and the bowel reserved for small concentrated nutrient enemata and the administration of medicine. Perhaps the best drugs to use in this way are chloral and the bromides in full doses. Morphine hypodermatically has certainly done good in some instances. This was notably true in my second case, where the narcotizing of the child seemed to be the means of saving his life. It should certainly be tried early in all bad cases. Stimulants by the rectum and strychnine and digitalis by the skin are to be used as needed. Hypodermoclysis is a treatment for severe cases which seems to offer the hope of benefit. Ice or counter-irritants to the epigastrium may be tried. As the disease advances, and especially if a lull in the vomiting occurs, it

is safe again to try to obtain a free action of the bowels by the administration by the mouth of repeated doses of phosphate of soda or Rochelle salts. This is on the principle that if the vomiting is an effort by nature to eliminate the poison from the system free drainage through the bowel may aid in accomplishing this end. But there is nothing to be gained at any time by a mere unloading of the bowel by enemata, as though the constipation were the cause of the vomiting.

DISCUSSION.

DR. STOCKTON: Dr. Griffith did not speak very particularly about the character of the vomiting. I have found in all my cases that the vomited matter, after the stomach has been relieved of its food contents, is practically pure gastric juice. It will respond to all the tests for gastric juice and is vomited in large quantities. One striking feature about it is that when improvement begins the hydrochloric acid disappears from the stomach contents. I cannot say, however, in what proportion of cases this disappearance occurs, but it is my belief that it is the rule.

A second matter that has attracted my attention is that, even in children, there is a periodicity in recurrence, and in that respect my experience differs from that of Dr. Griffith. In one child that I had under observation from five to thirteen years of age there was always two and usually three or four attacks in the year, which occurred in the third or sixth month intervals.

I wish to confirm Dr. Griffith's opinion that there is some difference between these cases and those described by Leyden. In children the apparent periodicity, the peculiar character of the juices vomited, the intense prostration, and the very rapid convalescence make it a very striking disease. I have seen no deaths and have never before heard of a child dying from this disease, and the deaths that are reported here it seems to me must have been accidental—the result of complications; for such an end is not to be expected.

DR. W. W. JOHNSTON: I have had the opportunity of seeing three cases of recurrent vomiting which in all essential points were like those reported by Dr. Griffith. One of these I watched from its early development until it ended in recovery, after an attack of scarlet fever, at the age of fifteen years. Another case, a child now twelve years of age, has been followed for five years past, a distinct improvement taking place from year to year. In both of these cases the recurrent attack of vomiting accompanied by great prostration has been the distinctive feature. The third case, one of recent origin, is peculiar in that from the very first attack the symptoms were of an alarming character; in the second attack, a few months after the first, the child

was exceedingly prostrated and at one moment appeared to be dying. In two of these cases there was the vomiting of altered blood in addition to the symptoms mentioned to-day. Another symptom that has not been spoken of is the cyanosis, with cold extremities and feeble pulse, that is associated with the latest stages of the attack. The apparent imminence of death is very marked, but just as the patient reaches the point of dying the improvement begins. All the children that I have seen were the offspring of nervous parents, were precocious, and the victims of child-neurasthenia. The association of preternatural mental development and recurrent vomiting is a constant one. The condition is not due to indigestion or cold, is not a simple catarrh, and is not prevented by methods that improve digestion. The development of a toxin, which may be the same as that concerned in the causation of neurasthenia, may be the cause of this disease. In all its essential features it is a toxæmia.

The treatment, in my opinion, that offers the greatest hope of benefit is one directed to the child's nervous system, with the view of retarding precocious mental development and improving general nutrition. In older children complete bodily rest for a time, or a modified rest treatment, is of service. The collapse symptoms with cyanosis are most quickly relieved by subcutaneous and rectal injections of normal salt solution. In the last case to which I referred the immediate effect of hypodermoclysis was marvellous, the patient's pulse growing stronger and the great restlessness subsiding almost immediately after the injection.

DR. KINNICUTT: I would like to say a word in regard to the treatment. The treatment I have found most satisfactory consists in the use of the saline solution. By this method you not only stimulate the circulation and heart in the most satisfactory way, but you supply the lack of water and bring about elimination through the kidneys if, indeed, you are dealing with a toxin. In giving the treatment by enteroclysis I use the solution at a temperature of 115° to 120°, or if by hypodermoclysis at a temperature of 110° to 112°.

DR. FORCHHEIMER: I have seen quite a large number of these cases, especially the milder ones, for I have seen only one that died. It has seemed to me that a careful study of these patients from infancy must make one reflect upon the presence of certain symptoms that seemed to be predominating in the intervals. In the first place, these patients are always constipated; secondly, they are always neurotic children, and, in the third place, in a majority of these cases the anatomical basis for constipation exists—that is, an exaggerated development of the descending colon, such as is found so often in children. These things combined lead one to conclude that this anatomical condition is the physical basis of the disease, the resultant of which would be, of course, that retained materials are absorbed into the circulation, and, as is so frequently the case, these are eliminated by the stomach and cause vomiting. Another thing that speaks in favor of this

view is the fact that as the colon develops—that is, from ten to fifteen years of age—the children lose this condition of recurrent vomiting. There is no doubt that there are other forms of cyclical vomiting besides this one. I have seen one case in which repeated attacks of intussusception, verified by autopsy, produced this symptom. Again, in some children it seems as if this symptom could be provoked purely upon a psychical basis. As to the treatment, so far as my experience is concerned, prophylaxis is most important, in that the aperistalsis ought to be relieved by all the means at our command.

DR. SHATTUCK: I would like to ask Dr. Griffith about the findings at the autopsy in his first case.

DR. GRIFFITH: There was an increase of the epithelium of the gastro-intestinal tract, with some degeneration of the glomeruli of the kidney, but not marked.

DR. SHATTUCK: I have had one fatal case which I suppose would come under this category. The child was very neurotic and very precocious mentally. After almost three weeks of obstinate and uncontrollable vomiting she died. Dr. Councilman made the autopsy, examining the brain and spinal cord. There was an extreme degree of fatty degeneration of the heart, liver, and kidneys, the most extreme, Dr. Councilman said, he had ever seen up to this time, but of not more than a few days' duration, he believed. It seemed some form of infection.

DR. GRIFFITH: I am very glad, indeed, that the paper has brought out so much discussion, because I felt sure that there must exist a much larger experience with the disease than the very meagre remarks in text-books would indicate. With regard to the character of the vomited matter, I would say that the only case I find reported in which an excessive secretion of hydrochloric acid is mentioned is that reported by Dr. Snow. Dr. Johnston's remarks express exactly my experience. I have spoken in detail of the matters in my paper, but have omitted them in my abbreviated remarks before you in order to save time. Dr. Trudeau has just asked me privately whether the condition is not allied to migraine. I should say yes. In one of the cases reported by Rachford migraine developed and the attacks of vomiting ceased as the child grew older.

Regarding the use of hypodermoclysis, to which one of the speakers has referred, I believe that this treatment may prove of value. In my first fatal case, the child of a physician, I urged that this treatment be tried if another attack occurred, but for certain reasons it was not done. It is perfectly true, as has been remarked, that it is well, if possible, to get ahead of the attacks by treatment in the intervals. To confine the child to bed, however, is out of the question. As there is no regularity in the occurrence of seizures, it is manifestly impossible to put the patient in bed for, perhaps, months or a year.

THE SANITARIUM TREATMENT OF INCIPIENT PULMONARY TUBERCULOSIS, AND ITS RESULTS.

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Many years ago circumstances placed me in a position where the problems connected with tuberculosis were of necessity daily before me, and afforded ample opportunities for the study of the disease in its clinical, scientific, and humanitarian aspects. The long time required to obtain a cure, or even an arrest, of the disease by the climatic and open-air method, and the necessary expenses it entailed, when added to the loss of income incident to months of enforced idleness, seemed to put the practical application of this method of cure beyond the reach of the majority of individuals who have to earn their own living. An institution that would offer this opportunity and a return to a life of usefulness to workingmen and women at a moderate cost seemed an urgent necessity, and induced me to attempt the establishment of such an institution and put the methods so long advocated by Brehmer to a practical test.

In view of the present wide-spread agitation on the subject of tuberculosis I have thought at this time some of the experiences and results obtained in the past fifteen years, while developing the first sanitarium in America for the treatment of pulmonary tuberculosis in persons of moderate means, might prove of interest.

In looking back it seems curious to note while every new consumption cure advocated has at once been eagerly taken up and tested, how slowly the rational teachings of Brehmer in regard to the treatment of the disease came to be generally accepted even abroad, while in this country the value of his methods is only now beginning to be realized.

I will not weary you with a detailed description of the Adirondack Cottage Sanitarium, its history, its struggle for existence, or its growth and development, but will merely touch briefly on a few points which relate to the class of patients it tries to cure or relieve, call your attention to a few features of the treatment, and lay before you the results obtained in the past fifteen years. My acknowledgments for valuable assistance and support are due to the late Dr. Alfred L. Loomis, to Dr. E. G. Janeway, Dr. Walter B. James, Dr. H. P. Loomis, and Dr. E R. Baldwin, who for many years have examined without remuneration applicants for admission to the institution.

The two requisites for admission are that the patient should be unable to pay the usual prices charged in the region and that he should be in the incipient stages of the disease. Five dollars a week has been the uniform charge to all alike; no graded rates or private patients; no charge for medical attendance, the deficiency in the running expenses being made up each year by subscriptions. It is a pleasure to me to state that during the past fifteen years not only has money enough to meet this deficiency been always forthcoming, but that the growth and development of the institution has been rendered possible by what has been put aside each year over and above the amount necessary to meet the running expenses, the plant paid for and entirely free from debt, and that enough has been saved to accumulate a Free Bed Fund of $18,000 and an Endowment Fund of $150,000.

Experience has shown most forcibly that the success of institutional treatment depends upon the early detection of the disease. It has been found that 68 per cent. of truly incipient cases were discharged as apparently cured, while only 11 per cent. of advanced cases recovered. We must recognize more and more the evident limitations of physical examination alone, and the dictum so often assumed that if nothing can be detected by this method the disease is not present seems to me utterly untenable. The pretubercular stage of tuberculosis so much written about is nothing more than the first stage of tuberculous infection before physical signs have appeared. In the first stages of miliary tuberculosis of the lungs there are no appreciable physical signs, and no physical examination can be expected to detect the onset of tuberculous infection in the glands or deep tissues and organs of the body.

In attempting to make an early diagnosis in obscure cases of late I have occasionally been assisted in reaching a conclusion by a careful X-ray examination, and, where it was necessary, by the tuberculin test. I have had on several occasions a practical demonstration that an examination with a good X-ray machine and the fluoroscope may in early cases be of service in affording additional evidence of the presence of the disease. The diaphragm is seen to be higher on the suspected side, or its excursion diminished on one or both sides, and in many cases a slight shadow can also be detected at the site of the suspected lesion. Of course, this may occur as the result of any other pathological condition which tends to diminish the expansive action of the lungs and impair their transparency, such as areas of pneumonic infiltration, bronchitis, etc., but if the history and rational signs are carefully considered these may generally be excluded.

If additional and more conclusive evidence is required the tuberculin test should be applied. By a resort to this test a positive opinion one way or the other can often be reached, and if the initial dose does not exceed one milligramme the constitutional disturbance caused by it is slight, and no injury to the patient has, in my experience, ever resulted from such a test. During the past two years I have seen several cases in which a slight impairment of health, without cough, physical signs, or appreciable rise of temperature, being the only symptom present, a diagnosis of tuberculosis was made possible by a study of the fluoroscope picture, and, if this proved negative, the application of the tuberculin test, the correctness of the diagnosis being confirmed later by the appearance of physical signs in the chest, of hæmoptysis, or of cough, expectoration, and bacilli. One case which I saw during the earlier part of last summer illustrates these points. Repeated physical examinations by experts of undoubted skill had been negative; the X-ray picture was inconclusive; there was no cough or expectoration, the only symptoms present being some loss of weight and strength, and a temperature which occasionally touched 99.5° in the evening. The gentleman being a physician and insisting on a diagnosis, I advised the tuberculin test.[1] Two milligrammes gave a typical reaction. He obtained a

[1] Koch's original tuberculin was used at the Sanitarium for a year after the announcement by this investigator of this new method of treatment. From that time, however, all the tuberculin has been produced at the Saranac Laboratory, and has been modified according to the

year's leave of absence and went West. A few months later he wrote me he had gained twenty pounds, and that no one believed he had ever had tuberculosis. Recently, I received a letter from him stating that one morning, after some unusual physical exertion the previous day, he had spit a teaspoonful of blood, and that on being examined by a physician he had been told that there was a slight pleuritic friction sound behind the right scapula.

The scope of this paper will not allow me to discuss the details of institutional treatment, of which the main factors are an invigorating climate; an open-air life; rest, coupled with a careful regulation of the daily habits; an abundant supply of nutritious food, with the exhibition of such tonic and restorative measures as may be indicated in each case. I think, however, the favorable influence of rest on the course of a tuberculous process is not generally recognized. Surgery has taught us that activity of a part affected with tuberculosis always tends to aggravate the disease and to render it progressive. A tuberculous joint may often be cured by simple immobilization, while it will go on to destruction if the patient be allowed to use it at will. In advanced tuberculous ulceration of the larynx, where it becomes necessary to perform tracheotomy, the rest afforded to the parts by the operation is at once followed by a remarkable improvement in the disease in the larynx. Murphy's proposed treatment, which consists in putting the diseased lung completely at rest by introducing nitrogen gas into the pleural cavity, is another proof of the recognition by the surgeon of the value of absolute rest.

Absolute rest, so long as it is taken in the open air, is the best measure at our command to reduce the pyrexia of tuberculosis, to

indications which the latest researches on this subject seemed to call for. For several years a tuberculin made like Hunter's modification B. was principally in use. The general plan of separating the albumoses from the culture fluid laid down by Hunter was adopted, except that no heat was used at any time in the process.

Before making an extensive trial of Koch's new TR tuberculin, it was thought best to study this substance in the laboratory. The researches made there by Dr. E. R. Baldwin and myself showed that samples of TR, as it was first put on the market, contained living tubercle bacilli, and for this reason the substance as then produced was considered unsuitable for the treatment of human tuberculosis. Dr. Baldwin has also recently shown that, although the directions accompanying the bottles of the new TR tuberculin state that it contains ten milligrammes of solid substance, if the water and glycerin be evaporated about four milligrammes only of solid substance remain.

During the past year Hahn's tuberculo-plasmine, made after the method of Buchner and Hahn, of crushing the bacteria with excessive hydraulic pressure, has been used in a limited number of cases

conserve the patient's energies, to abort the activity of the process, and encourage the formation of fibrous tissue about it. The objection that a patient cannot digest if he does not exercise does not seem generally to be supported by experience, as most of the patients, while living out-of-doors and kept absolutely at rest, eat and digest an amount of nourishing food that would suffice for laboring men.

Specific methods of treatment have been very little used at the Sanitarium, with the exception of tuberculin, which has been employed with the utmost care for the past eight years, in selected cases, in order that some evidence as to its healing or immunizing influence, when given under the most favorable conditions of environment, might be obtained. Tuberculin treatment is apparently injurious rather than beneficial in all those forms in which the disease is actively progressing or where there is any marked fever or constitutional impairment. It is evident that the addition of more toxin to an organism already unable to cope successfully with that produced by the disease would not be likely to be beneficial. Such treatment would find a parallel case in an attempt to produce immunity by injecting more diphtheria toxin in the case of a child with diphtheria already overwhelmed by the poisonous substances elaborated by the germs.

The exhibition of tuberculin has been confined at the Sanitarium to apyretic cases, or those that were nearly so, if well nourished and with moderate lesions, the diagnosis of the disease being confirmed in every case by a microscopical examination of the expectoration. The treatment should be begun with a minimum dose, very gradually increased, and with lengthening intervals, so as to avoid the production of constitutional symptoms, except, perhaps, occasionally a slight rise of temperature, and continuing the injections for several months, until no general reaction is produced even by large doses; the nutrition of the patient being closely watched, and the injections continued only so long as the weight is kept up and the nutritive condition remains at a high standard. In other words, the aim being to produce repeated local reactions with but slight or no general reaction, and gradual habituation to the tuberculin toxin. The doses and the interval between them should be carefully adapted to the needs of each case, and the best results by this method are obtainable only with care, patience, and skill. Time is also an important element, and my experience has seemed to confirm that of Petruschky in so

far as necessity of repeating a course of injections after an interval of several months, when susceptibility to reaction has returned. The reason for this is obvious when we reflect that all tuberculous foci in the body are not at the same stage of their development when the treatment is begun. When applied with care, avoiding the production of violent reaction and high fever, I have never seen any evidence that would lead me to think that the treatment had proved injurious at any time to the patients who were subjected to it.

Time will not allow me to discuss the various opinions held as to the nature of tuberculin reaction or the question of artificial immunity in this disease, but I will merely lay before you, so far as it can be done by figures, the results of the application of this treatment to the human subject under the most favorable conditions of environment, in so far as they relate to any apparent curative influence of the injections and to any immunizing effect as shown by the prevention of relapse. I have selected only the cases treated since 1894, as before that the details of the method were less understood, and it was often only temporarily applied. Since 1894, 56 cases have been treated by this method. It has been possible to follow the results in only 50. Of these I have taken only the incipient cases, so as to avoid as much as possible errors of classification, although the results in the cases classed as advanced were proportionately somewhat more favorable.

There were 24 incipient cases, and of these, 20, or 83 per cent., were discharged as apparently cured. For comparison, if we take the last 113 incipient cases treated at the Sanitarium by climatic and open-air methods alone during the past three years, 82, or a little over 72 per cent., were discharged apparently cured; so it would appear from these figures that tuberculin had had some favorable influence on the results. Some little allowance, however, must be made for the fact that, even though all these cases were classed as incipient, those treated with tuberculin were selected with special care. In order to procure some evidence as to the immunizing effect of this treatment and its power to prevent relapses, an attempt has been made to trace 50 apparently cured tuberculin-treated cases, and for comparison 50 untreated cases which corresponded as exactly as possible in point of classification on admission and discharge, and which were in the institution at the same time and remained the same length of time, have been studied, with the results shown in the following tables:

TREATED.

Not traced		3
Remained well:		
Returned to work in former surroundings	29	
Living out-of-doors life in other good climates	7	
Not working	5	41
Relapsed (living)		1
Relapsed (dead)		4
Died, insanity		1
Total		50

NOT TREATED.

Not traced		3
Remained well:		
Returned to work in former surroundings	21	
Living out-of-doors life in other good climates	10	
Not working	5	36
Relapsed (living)		6
Relapsed (dead)		5
Total		50

Of the 50 tuberculin-treated cases discharged apparently cured at varying periods since 1891, 3 could not be traced and 41 remain well to this date. If we take 50 untreated patients who were also discharged apparently cured at the same periods of time, and leave out 3 to correspond with untraced tuberculin-treated cases, 36 up to date are known to have remained well. These figures show a slight percentage in favor of the tuberculin cases, but unfortunately are not sufficiently marked to be in any way conclusive.

My experience with tuberculin treatment at the Sanitarium thus far has led me to believe that when carefully applied in suitable cases it has proved apparently free from any danger, and that it has seemed to have some favorable influence in bringing about healing of the lesions, probably by inciting the formation of fibrous tissue. In this it resembles Landerer's treatment by injections of cinnamonate of soda, this substance producing a local general leucocytosis, and stimulating the formation of fibrous tissue around the tubercle, and thus tending to limit the disease. That a certain reaction of the tissues, as shown by vascular hyperæmia and leucocytosis, is capable of favorably influencing a tuberculous process is shown in the cure of peritoneal tuberculosis by laparotomy, which occurs as the result of

the hyperæmia of the tissues brought about by the traumatism of the operation and their exposure to the air.

The immunizing effect of tuberculin as observed in the human subject would appear to be more uncertain both as to degree and duration, and artificial immunity is still the unattained goal of experimental research. While the evidence as presented by the cases treated with tuberculin at the Sanitarium is somewhat favorable to this form of treatment, it is restricted as yet to a very limited number of cases, and it must be admitted that these are usually such as are likely to recover under climatic and open-air methods alone.

The exact results obtained at the institution by the combined climatic and sanitarium treatment are difficult to express in figures, because they are generally influenced by the class of cases accepted. With advancing familiarity with the disease, and improved methods of diagnosis, our standards have also steadily altered, so that what would have been considered an incipient case fifteen years ago would be classed as an advanced one to-day in most instances. Furthermore, the term "cure" can also be used only in a relative sense, time as measured by years being the only criterion of cure. Of late the results obtained have been better than formerly, and this is due, no doubt, not only to improvements in methods and plant, but to the fact that more really favorable and early cases are available than formerly.

In making out the yearly reports of the institution I have adopted from the first, and printed in each report, the following classification, imperfect as I feel it to be, as the best I could devise to express the classes of patients admitted and the results obtained:

Definition of Terms Employed.

1. *Incipient.* Cases in which both the physical and rational signs point to but slight local and constitutional involvement.

2. *Advanced.* Cases in which the localized disease-process is either extensive or in an advanced stage, or where, with a comparatively slight amount of pulmonary involvement, the rational signs point to grave constitutional impairment or to some complication.

3. *Far Advanced.* Cases in which both the rational and physical signs warrant the term.

4. *Apparently Cured.* Cases in which the rational signs of

phthisis and the bacilli in the expectoration have been absent for at least three months or who have no expectoration at all; any abnormal and physical signs remaining being interpreted as indicative of a healed lesion.

5. *Arrested.* Cases in which cough, expectoration, and bacilli are still present, but in which all constitutional disturbance has disappeared for several months, the physical signs being interpreted as indicative of a retrogressive or arrested process.

An idea of the best results obtained thus far can, perhaps, be gained by a glance at the following table, copied from the last three annual reports, 1897–98–99, provided the figures are considered together with the classification adopted. Patients who have remained less than three months are put in a separate class, as little can be accomplished in the way of permanent results while in the institution for so short a period:

TABLE.—323 Patients who Remained an Average of 8¾ months.

Condition of patient when admitted.	Apparently cured.		Disease arrested.	Improved.	Unimproved or failed.	Died.
113 incipient cases	82	72.566 pr.ct.	25	4	2	0
151 advanced "	27	17.88 "	67	43	13	1
59 far " "	0		12	26	16	5
323 total.	109	33.746 pr.ct.	104	73	31	6

A glance at the table shows the following results: Out of 323 patients who remained an average of eight and three-quarter months in the institution, 113 of which were classed as incipient cases, 151 as advanced, 59 as far advanced, 109 were discharged apparently cured, 104 with the disease arrested, 73 improved, 31 unimproved or failed, and 6 died. This gives the best results as yet attained at the Sanitarium—*i. e.*, 33 per cent. of apparent cures, and 32 per cent. of cases in which the disease was arrested.

If we study the gross results on the 1200 patients admitted during the past fifteen years, the result is as follows:

23 per cent. were discharged as apparently cured.
56 " " " with the disease arrested or much improved.
19 " " " as stationary or unimproved.
2 " died in the institution.

I am quite aware that cure in tuberculosis is but a relative term, and that time is the only test of cure, a test which becomes more and more discouraging as the period of the application lengthens and we become more familiar with the relapsing nature of the disease. Nevertheless, I have attempted, with Dr. E. R. Baldwin's assistance, to determine as far as was practicable, the permanency of the results obtained, extending over a period of fifteen years to date. Of the 1176 patients discharged alive about one-half are still living, and one-half of this number are heard from as being perfectly well. This proportion of one-quarter of the whole number covers the entire fifteen years, and the percentage, of course, improves each year as more early cases are admitted. The permanency of the recoveries depend necessarily a good deal on the environment to which the patient returns. If he is obliged to go back to a laborious life or an in-door occupation he is much more likely to relapse than if it is possible for him to return to a good climate and an out-door existence.

The education which the patients receive at the Sanitarium as to the nature of their disease and the methods to be relied upon in combating it is of the utmost value to them, enabling them to preserve their health and avoid relapses after they have left the institution; and this education is not limited to themselves, but is imparted by them to the great mass of people with whom they come in contact.

In addition, the attempt to cure pulmonary tuberculosis by institutional treatment, and the practical demonstration which it has given of the possibility of accomplishing this in many cases, has cast a ray of light on one of the darkest problems which confronts medical science, and has proved an object lesson which has, perhaps, not been without influence in creating the present popular demand that the State supplement private philanthropy in the establishment of similar institutions under its control.

DISCUSSION.

Dr. Bridge: I had supposed that the statistics of the use of tuberculin were a little more extensive than they are, and that benefits from the careful use of it would show a little better in the statistics than they do; but I believe we may take the statements of Dr. Trudeau as absolutely reliable. From his experience, careful as it has been, it seems to me we are hardly

justified in using tuberculin very much in the treatment of tuberculosis. If we could have for our cases all the other attentions that he gives his patients, and that all patients with tuberculosis should have, we might resort to tuberculin in the careful manner he has indicated; but the trouble is that every time we begin to use it or serums we are apt to neglect other measures that are so much more useful.

I applaud what he says of the general significance of tuberculosis in his sanitarium. It is surprising that it has taken us so long to discover that the great measures for tuberculous patients are fresh, pure air, if fever is present absolute quiescence and freedom from exercise, both mental and physical, and abundance of nourishment. In private practice we ought to try and produce the sanitarium management. Three-quarters of our patients could probably be managed more nearly along such lines, and a great deal better than they are managed, if we made a decided effort. This is important, for most of our patients cannot be treated in institutions. We find physicians frequently advising their patients to stay in close rooms and avoid the night air, and they allow them to eat such food as their whim pleases, and even order free exercise even when their temperature is above normal every day. Exercise is wrongly advised, on the theory that without it the digestion will go wrong, or on the theory that exercise makes vigor. Both are wrong; the quiescent patient will digest large quantities of food if taken in the right way, and the only vigor much worth cultivating is resisting power to tuberculosis, not capacity in gymnastics.

Dr. Solomon Solis-Cohen: There are two questions I should like to ask in order to get additional information. I should like to know upon what Dr. Trudeau and his consultants depend to recognize tuberculosis before the physical signs or fluoroscopic signs are sufficiently advanced to give positive evidence; and whether, in referring to rest, Dr. Trudeau advises enforced local rest of the lung as well as general rest of the body. In my own experience enforced local exercise of the lung is usually of much advantage, except in cases with active softening or with persistent high temperature; while, of course, in such cases as Dr. Trudeau refers to, proper alternation of general rest and general exercise needs to be insisted upon. I have for more than ten years publicly advocated prolonged rest in the open air for febrile cases.

For the general profession I think that the lesson to be drawn from Dr. Trudeau's experience with tuberculin is that tuberculin should only be used by Dr. Trudeau and men like him. I have recently had occasion to summarize this question, and I believe Dr. Trudeau's remarks justify the statement I made, that "its disadvantages are so positive and its advantages so dubious that it should be used only with the greatest caution by the most skilful hands."

Dr. Trudeau: In making an early diagnosis I think the rational signs, as a rule, are not studied sufficiently. A careful temperature-record taken

for one or two weeks, three times daily, will help materially in making a diagnosis, a thing which is rarely done. A slight occasional evening rise to 99.5° or 100°, when accompanied with some evidence of impairment in the general health, is a suspicious symptom. I recall a case I saw in a Boston hospital recently with Dr. Williams, while studying with him some of his X-ray pictures. He selected a boy who had been in the hospital for a week with symptoms of indigestion, in order to show me the appearance presented by normal lungs with the fluoroscope. I glanced at the chart hanging over the boy's bed, and noticed that his temperature during the week had reached 99.5° on one evening and 100° on another. I suggested that this, to my mind, was suspicious of tuberculosis. When examined under the fluoroscope there was a slight shadow at the right apex, and the excursion of the diaphragm on that side was markedly diminished. We gave him tuberculin, and the next day his temperature reached 102°, confirming the diagnosis of tuberculosis, although no other symptom had been present, but an almost unappreciable deterioration of health and a slight evening rise of temperature.

We need, I think, further information in regard to the tuberculin test as relates principally to its reliability, its limitations, and its possible dangers. In cases in which I have used it I have never seen it light up a new process, but it is evident that it is not proper to use it in all cases, especially in those running a high temperature. It is a noteworthy fact that there is little or no experimental evidence bearing on the possible dangers of the tuberculin test. I tried this winter to get some evidence on this point, and to determine whether the assumption that the tuberculous process is scattered by the tuberculin test was borne out by experimentation. My first experiments bore on the duration of life in guinea-pigs, but there was no shortening of the life-period in those that took the tuberculin. I made another interesting experiment in order to determine whether the tuberculin test caused the spread of a localized tuberculous process. Twenty rabbits were inoculated in the cornea, and after three weeks all the animals presented a tuberculous ulcer of about the same size. Ten of these received doses of tuberculin sufficient to cause reaction on four occasions. After a lapse of eight weeks a comparison of the eyes of the controls and tested animals showed no evidence of spread of the process in those which had received the tuberculin.

In attempting to rest the lung I have never tried Dr. Murphy's suggestion, but have confined myself solely to keeping the patient at rest. This is necessary only where there is temperature, and the degree of rest should be guided by the symptoms. I feel strongly, however, that the regulation of the daily life of the patient is of the utmost importance to him, as in this way many of the relapses usual to most cases may be avoided and the case ultimately carried to a favorable issue.

ON THE ORIGIN OF OXALURIA FROM FERMENTATION IN THE GASTRO-ENTERIC TRACT.

COMMUNICATION BY C. A. HERTER, M.D., OF OBSERVATIONS MADE IN HIS PRIVATE LABORATORY BY HELEN BALDWIN, M.D.

OXALURIA is a symptom which has forced itself upon the attention of clinicians ever since Donné, in 1838, discovered calcium oxalate crystals in the urine. The importance of the condition was exaggerated by the early observers in their conception of an "oxalic acid diathesis." In the latter part of the century, on the other hand, it has been considered to be of little consequence. Yet the subject has continued to be of interest, because there has never been definitely determined what was the origin and significance of the oxalic acid found in the urine when present in large amount.

It was early noted that the ingestion of foods rich in oxalates led to the excretion of an increased quantity of oxalic acid. This is notably true of rhubarb. Esbach and Auerbach, making analyses of common foods, found oxalic acid in a large number of vegetables, grains, and fruits, as well as in tea and coffee, so that in an ordinary mixed diet oxalic acid is always present.

Dunlop, in a paper published in 1896, supported the view that all the oxalic acid which appeared in the urine had been ingested with the food, and that oxalic acid was never formed in the animal organism by metabolism. His proof of this lay in the fact that when patients having oxaluria were placed on a milk diet oxalic acid was no longer found in the urine. It was with the purpose of testing the accuracy of this work of Dunlop's that the series of observations presented in this paper was made—that is, the object of the work was to determine whether oxalic acid was ever formed in the animal body, or whether the excretion of a large amount of calcium oxalate indicated merely an excessive ingestion of oxalic acid in the food or an increased absorption of the same from the alimentary canal.

The first work in this series of experiments consisted in the analyses of foods, in order to establish a dietary which should be free from oxalic acid and yet contain a greater variety of food than Dunlop's exclusively milk diet. The diet list found to be free from oxalates consisted of proteid food (milk, meat, and eggs), with butter, sugar, corn-meal, rice, and the Huntley & Palmer breakfast biscuits.

The method used in the quantitative analyses of the urine for oxalic acid was that described by Dunlop. This differed essentially from the older methods of Neubauer and Schultzen, in that the calcium oxalate was precipitated from an acid solution by means of alcohol, instead of from an alkaline solution by the use of calcium chloride or calcium hydrate.

In observations to determine merely the presence or absence of oxalic acid, without estimating its amount, the urine was mixed with 95 per cent. alcohol and allowed to stand until the calcium oxalate, if present, was precipitated. The sediment was then separated with the centrifuge and examined microscopically.

The first experiments made were upon the influence of varied diets upon the excretion of oxalic acid. In the analyses of twenty-four normal specimens from persons receiving a mixed diet, the daily amount was found to vary from mere traces to 34 mg. in a case where rhubarb was taken. The average normal amount was about 10 mg. daily, this being about half the average Fürbringer found in the specimens which he examined. The diet in certain cases was varied, being at one time rich in carbohydrates, at another time rich in proteids, and, again, containing a large amount of oxalic acid. The total daily excretion, however, varied but little, excepting that rhubarb caused a definite increase in the amount. It was found, also, that in cases where a diet free from oxalates was given, the results accorded with those of Dunlop—that is, oxalic acid, if present at all, was found only in traces. The urine of patients suffering from various diseases was also examined, and it was found, in the most of these cases, that when placed on a diet free from oxalic acid the calcium oxalate disappeared from the urine. A striking illustration of this was the case of a patient of Dr. Lambert's, who was subject to attacks of renal colic. When on a mixed diet, including rhubarb, the oxalic acid excreted in twenty-four hours was 67.5 mg. When on a diet free from oxalates for four days it fell to 4 mg.

A marked contrast to the usual disappearance of oxalic acid on a diet free from oxalates was found in two cases of nervous depression, which were in the care of Dr. Hallock, of Cromwell, Conn. One of these was a patient in a melancholic condition. She was very irritable, had headache, digestive disturbances and poor sleep. After being for a week on a diet free from oxalates she still excreted 25 mg. of oxalic acid in a day, this being about twice what had been found to be a normal average. Another patient had some digestive trouble with headache and was full of nervous fears. In this case, also, after a week on the same restricted diet, 25.5 mg. of oxalic acid were excreted in twenty-four hours. These two cases, in contrast to all others examined, indicated that some cause other than the food ingested was influencing the oxalic acid excretion.

In addition to these clinical observations numerous studies were made upon dogs, the results of which accorded with those noted in man. When the animals were placed upon a diet of meat or milk, oxalic acid was not excreted in the urine. It was found, however, that in the case of a dog given a very large amount of sugar, over a long period of time, that the result was different from that noted in normal dogs. The animal placed under observation was given all the sugar that it would take. It ate the sugar greedily, at times receiving from 200 to 300 gms. in a day. For a month the animal showed no symptoms. It increased in weight and seemed healthy. After about six weeks there appeared simultaneously a group of symptoms consisting of loss of appetite, vomiting of a frothy mucus, an intermittent diarrhœa, an absence of free hydrochloric acid in the gastric juice, the presence of organic acids in the urine, and with these the appearance of an abundant precipitate of calcium oxalate crystals in the urine. For two months the dog had been on a diet free from oxalates, so there seemed no question that the oxalic acid was formed in the body. This dog was kept under observation for three months with an almost constant excretion of oxalic acid in the urine. The same experiment with sugar was repeated on two other dogs with the same result.

Having determined that oxalic acid was formed in the animal organism, the question naturally followed as to where and how it was produced. Neubauer suggested that it might be formed in the alimentary canal, and this view has been supported by Bouchard and Ellis; but the majority of writers on oxaluria have believed that oxalic

acid was formed in the tissues through a defective oxidation, probably due to a direct nervous action upon the cells.

In the case of the dogs which were studied it was found that when a mixture of meat and sugar was fed to them, and the stomach contents withdrawn an hour after feeding, oxalic acid had already been formed in the stomach. It was further noted that when a small portion of the stomach contents from the dogs with oxaluria was used as a ferment and added to a solution of sugar and beef extract, oxalic acid was formed in the mixture. This experiment was repeated, using as a ferment a portion of the stomach contents of a patient with oxaluria. In this case, also, oxalic acid was formed by fermentation.

As a result of this series of experiments, the following conclusions have been reached:

1. That in health there is little or no oxalic acid formed in the body, but that which appears in the urine has been ingested with the food.

2. That in certain morbid conditions, which in the cases noted above were associated with the absence of free hydrochloric acid in the gastric juice, oxalic acid is formed in the stomach and is probably due to an organized ferment.

DISCUSSION.

DR. TYSON: Naturally, in the course of my experience, I have seen a great many cases in which oxalate of lime has been a factor in urinary analysis. I must admit, however, they have been chiefly cases wherein the oxalate of lime has been a sediment in the urine, and there have been no special efforts made to extract it when it was not thus demonstrable. The sum of my experience clinically is that I have been unable to find any definite condition associated with the presence of oxalate of lime. In the vast majority of cases it gives rise to no symptoms. I have had a few patients in whom it was an unfailing sediment. These, too, had no symptoms in any way ascribable to it.

I have also made many efforts to influence the amount of oxalate of lime in the urine of such cases. The only treatment I have found to be invariably followed by a total disappearance of the sediment is a milk diet. I have never placed patients upon a pure proteid diet with a view to determining its effect, but I would have expected that such *a diet would not be attended* by a disappearance of the oxalate of lime, as Dr. Herter's experiments seem to show. It is well known, of course, that vegetable food is more likely to increase the amount of oxalate.

EXPERIMENTAL RESEARCH SHOWING THAT URIC ACID SECRETION IS NOT REGULARLY DIMINISHED IN THE PERIOD PRECEDING EPILEPTIC SEIZURES.

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AND

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THE toxic theory of disease-processes, and especially of the periodical and occasional neuroses and psychoses, has so warmly commended itself to the minds of physicians of our generation, and has been utilized with such eagerness as a basis of therapeutics, that sufficient pause has not often been made to ascertain whether the data on which the clinical statements have been based would stand the searching test of really accurate and critical analysis.

For my own part, I believe that the point of view itself has often been wrong, and that, at least so far as the neuroses and psychoses are concerned, it may prove that the toxic theory of their pathogenesis should take a subordinate place, and that a more fruitful line of research would be one that looks on these affections as caricatures of normal states, their peculiarities being expressible, no doubt, in chemical terms, but better, it may turn out, in those of physiological reaction or anatomical structure.

This search for toxic causes has naturally been especially active with regard to epilepsy, and has been held by many observers as representing, indeed, the only rational outlook for an explanation of its symptoms, though of late the "inhibition" theory, as expressed,

among others, by Oddi, the Italian physiologist, has been advanced as a promising alternative.

One of the most recent supporters of the toxic theory of epilepsy is Kräinsky, a Russian physician and chemist, who has made several long series of apparently painstaking experiments, the results of which are recorded in the *Zeitschrift für Psychiatrie*, 1898, and elsewhere. This paper opens with the very positive and reiterated statement, on which, indeed, the final reasoning and conclusions are based, that the excretion of uric acid is invariably diminished before each outbreak of "idiopathic" epilepsy, the diminution sometimes immediately preceding the attack, sometimes being separated from it by an interval of normal excretion for a day or two. Immediately after the seizures the uric acid excretion rises again, he says, to above the normal, so that the total excretion for the whole period equals the normal quantity. He does not agree with Haig in thinking this substance to be the direct cause of the attack, but regards the variations in its excretion as corresponding to other chemical changes, through which the real poison is formed. For him this poison is carbaminic acid, but into the soundness of this hypothesis we shall not here attempt to enter.

Having been interested for some time past, together with Dr. Pfaff, in studying the uric acid question, I asked him to test the validity of Kräinsky's statement as to the invariable diminution of the excretion above referred to, which, if proved to occur, would be a very important fact, as showing that the epileptic attack is led up to by changes in general metabolism.

The research does not cover a large number of cases, but so far as it goes it is accurate. Not only were the analyses made by an assistant especially trained for the work, and under Dr. Pfaff's personal supervision, but control analyses were made in every instance, and all results rejected which were not thus confirmed, except in two instances.

The urines were sent to Dr. Pfaff daily from the Massachusetts State Hospital for Epileptics, at Monson, through the kindness of the Superintendents, Dr. Owen Copp and Dr. Everett P. Flood, to whom we express our sincere thanks.

The method of analysis followed was the Ludwig-Salkowski—the one now regarded as the best.

Patient.	Date.	Seizure.	Amount of urine.	Uric acid by first analysis.	Uric acid by control analysis.	Average.	Amount of uric acid in 24 hrs.
*[1] Case one	Oct. 22, 1899	Before	1370 c.c.	0.0641	0.0620	0.063	0.431
* " "	" 23, "	"	2810 "	0.0309	0.0288	0.029	0.419
* " "	" 24, "	Seizure.	520 "	0.0618	0.0560	0.059	0.153
* " "	" 25, "	None	1670 "	0.0159	0.0121	0.014	0.116
* " "	Nov. 26, "	Seizure	2100 "	0.0313	0.0272	0.0293	0.307
* " "	" 27, "	None	1710 "	0.0532	0.0500	0.0516	0.441
* " "	" 28, "	"	530 "	0.1408	0.0270	0.0339	0.355
* " "	Dec. 2, "	"	1260 "	0.0992	0.0904	0.0948	0.597
* " "	" 3, "	"	2260 "	0.0432	0.0428	0.0430	0.486
* " "	" 4, "	"	1390 "	0.0382	0.0372	0.0377	0.262
* " "	" 5, "	Seizure	1100 "	0.0770	0.0740	0.0755	0.415
* " "	" 6, "	None	1870 "	0.0562	0.0527	0.0544	0.509
* " "	" 7, "	"	1290 "	0.0900	0.0820	0.0860	0.554
" "	" 18, "	Seizure	1170 "	0.015	0.011	0.013	0.120
" "	" 19, "	"	870 "	0.014	0.012	0.013	0.087
" "	" 20. "	None	1500 "	0.020 + (0.2016 g. precip. out) =			0.426
* Case two	Oct. 21, "	None	1260 "	0.0813	0.0795	0.0804	0.506
* " "	" 22, "	Seizure	900 "	0.1314	.....	0.1314	0.591
* " "	" 23, "	None	2120 "	0.0514	0.0540	0.0527	0.558
* " "	" 24, "	Seizure	1640 "	0.0749	0.0481	0.0615	0.504
* " "	" 25, "	None	680 "	0.1690	0.1804	0.1747	0.593
* " "	" 26, "	"	1260 "	0.0526	0.0446	0.0486	0.306
" "	Apr. 24, 1900	"	1275 "	0.0550	.....	0.0550	0.522
" "	Apr. 25, "	"	1600 "	0.026	0.025	0.0255	0.30
" "	" 26, "	"	1110 "	0.037	0.033	0.035	0.28
" "	" 27, "	"	1060 "	0.030	0.029	0.0295	0.23
" "	" 28, "	"	1135 "	0.017	0.010	0.013	0.10
" "	" 29, "	Seizure	1150 "	0.022	0.019	0.025	0.17
" "	" 30, "	None	540 "	0.0081	0.0080	0.008	0.032

In all, twenty-nine specimens of twenty-four hours' urine were analyzed, coming from two patients. The first patient had five seizures during the period (three months) corresponding to the

[1] All the analyses marked in the table by an asterisk (*) were done by the older method of analysis as given in Hoppe-Seyler's Handbuch der chemischen Analyse, Berlin, 1893, p. 358.

All the analyses not so marked were done by the same method, with a slight modification, as given in Salkowski's Praticum der Physiol. u. Path. Chemie, 1893, p. 239

analyses; the second patient had two seizures during one month (October), and one seizure during another month (April). The results, as may be seen by examination of the accompanying table, cannot be said to bear out Kräinsky's categoric statements, either as regards the low excretion before the attacks or the high excretion after them.

In two instances the amount was very low, both on the seizure day and the day following, perhaps corresponding with the patient's presumably reduced state, or, indirectly, to a diminished ingestion of food. If there is any general conclusion to be drawn from the figures it is that the uric acid excretion of both patients was lower than that usually seen.

A reliable determination of the conditions of uric acid excretion taking place literally just before epileptic attacks must always be attended with difficulty, not so much because it is hard to anticipate the seizure as because the amount of excretion varies considerably for the different parts of the day and with the varying character of the food.

It seemed to us that the best way to begin, at all events, would be to examine a continuous series of twenty-four-hour specimens, to ascertain whether uric acid excretion was different on seizure days from that on free days. We did, however, in one or more instances, examine antiparoxysmal specimens, but without finding such differences as encouraged to further pursuit of this method.

MINOR FORMS OF CARDIAC DILATATION.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK.

Cardiac dilatation in a pronounced degree, due either to organic valvular disease or to obvious myocarditis—acute or chronic—is no doubt recognized and properly treated by the average good and careful clinician. This affection in its minor degree is frequently confounded with some other ailment, or when recognized not given its due importance, and hence ignored so far as active, direct treatment is concerned. Cardiac dilatation when at all advanced may usually be recognized, as we know, by the usual methods of physical examination.

Percussion shows increased cardiac dulness, especially in a lateral direction; palpation finds the heart impulse lessened in force, more diffuse, and the locality of the apex-beat often somewhat changed, and not always readily determined. Inspection corroborates these findings more or less well. The use of the stethoscope in addition reveals feeble, irregular heart sounds. The two sounds of the heart resemble one another more nearly—the long pause is shortened. We may or may not have a soft, blowing murmur at the apex of the heart, and this murmur, usually systolic, may also be diastolic. The pulse is rapid, irregular, depressible, as a rule. It may be very infrequent. Dyspnœa, palpitations, and occasional præcordial pain as symptoms of cardiac dilatation are not unusual. Now and then we have in most pronounced cases blueness of lips and fingers, obstructed general venous circulation, and œdema of the lower limbs. The foregoing is a brief picture of cardiac dilatation in its advanced stage.

As I meet it in minor forms in my daily rounds of practice it does not appear precisely after this manner, and I have been often

misled as to its presence and significance. One very ordinary type is that of the anæmic girl just past the age of puberty. She suffers often from too profuse menstruation, constipated bowels, and gaseous eructations from the stomach; she has little or no appetite, and is constantly tired and nervous. The heart fluttering and irregularity (subjective) which go with these symptoms we recognize, and yet how seldom do we consider the heart action in these instances as being indicative of organic change which must be treated properly and effectually if we are to obtain good, curative results. Such cases require iron and oxygen, rest and massage, proper diet and restricted hours of mental effort. They also require, still more—and in the beginning of treatment it is absolutely essential—small, repeated doses of digitalis and nux vomica until their hearts respond forcibly or at least with power sufficient to enable us to make satisfactory use of the other means to restore bodily activity. How shall we recognize such cases? Oftentimes with much difficulty, unless we appreciate rather obscure clinical facts. There is no diffuse or weakened cardiac impulse. On the contrary, the heart apex beats in the fifth interspace below and inside the nipple line. It may be of good force and not at all irregular. Abnormal sounds are not always present. There may not be any marked accentuation of the second sound. As a rule, however, the action of the heart is more frequent than normal, and the first sound is exaggerated, seemingly irritable. Give these patients for a week or two digitalis and strychnine in moderate doses, and follow them with a prolonged course of iron, and we get our best results. Act differently, and we are disappointed in our effort, time and again, to relieve symptoms and improve the general health.

One of the proofs, as I believe, which show the correctness of my diagnosis is that frequently in these cases the urine is light colored, of low specific gravity, containing neither albumin nor casts, and it may or may not be in sufficient quantity. Rest in bed will change this urine so far as color, density, quantity, and the elimination of urinary solids are concerned. It will also be effected and more rapidly sometimes with rest, sometimes without, by the use of suitable cardiac tonics in very moderate doses.

I know such a condition is often attributed to impairment of the nervous tone, or perhaps to hysteria. So, indeed, it is at times, but

behind this frequently is the loss of a certain amount of cardiac, muscular power. The cavities of the heart are doubtless slightly enlarged, and particularly that of the left ventricle, and the walls thinned. There is no hypertrophy, and why? Simply because there is not sufficient vital energy to produce it. The power of the heart can only be increased in one of two ways: by general corroborant treatment, or, at first, by suitable cardiac stimulation, and subsequently followed by the second. The latter plan is the speedier and better one, as I believe.

Formerly in some of these cases I was at times in reasonable doubt for a while as to whether I had to do with beginning renal changes of interstitial nephritis. The age of the patient, the anæmic state, and the rapid effects of judicious treatment settle all reasonable doubts very soon at the present time in the great majority of cases. In these instances is the heart muscle structurally affected? Is there granular or other degeneration of cardiac fibres? I do not believe so, at least in the great number of examples, in view of the success of treatment after several weeks or months. In other instances where there is little or no favorable response to rational medication, change of air and nursing, and where the examination of the blood by an expert shows signs that indicate a formidable anæmia feigning the pernicious form, I am convinced that we have to do with parenchymatous changes of the myocardium of more or less grave import.

Is there any method by which we can demonstrate these changes to the skeptical during life? Certainly not. All we can do is to reason from analogy and our pathological findings in more serious states which go on to a fatal termination. Fortunately, the overworked shop-girl, or the tired-out society young lady, when she gets the care required, ultimately, and as a rule, gets fairly well. I have no doubt in my own mind that in many instances perfected development or full growth of body reached from the twentieth to the twenty-fifth year explains the happy termination of some cases. In other words, these cases in a measure may be self-limited. To the unconvinced listener who would call such cases merely functional, I would answer: if they are, then the words of Sir Andrew Clark apropos of another topic seem to be singularly suggestive and true:

"We are," writes Clark, "so much concerned with anatomical changes; we have given so much time to their evolutions, differen-

tiations, and relations; we are so much dominated by the idea that in dealing with them we are dealing with disease in itself, that we have overlooked the fundamental truth that these anatomical changes are but secondary and sometimes the least important expressions or manifestations of states which underly them. It is to these dynamic states that our thoughts and inquiries should be turned; they precede, underly, and originate structural changes; they determine their character, course, and issues; in them is the secret of disease, and, if our control of it is ever to become greater and better, it is upon them that our experiments must be made." [1]

Another form to which I would direct attention is that of the somewhat obese woman—married or unmarried—between forty and fifty years of age. Not infrequently these women have a marked rheumatic tendency. Not infrequently their urine on cooling deposits an excess of urates or uric acid. They often have slight attacks of bronchitis, ambulatory neuralgic pains, localized dry pleurisy. When in their usual health they can take moderate exercise without great distress. So soon as they have any acute ailment or depletion they suffer from marked difficulty of breathing, a gone feeling at the epigastrium, and an inward sense of suffocation, as they express it. Usually their cardiac action is feeble, rapid, and slightly irregular under these circumstances. Physical examination may or may not reveal at this time a soft, blowing murmur—systolic as a rule, often heard with greatest intensity in the mitral area, but also heard at times in the left intercostal spaces above the nipple or at the lower end of the sternum. The blood may or may not show a moderate degree of anæmia. During and after their menstrual epochs these patients are often at their worst, and whenever the flow is abundant their condition inspires great solicitude. They do not always have fever when they have their slight bronchitic or pleuritic attacks. At other times the temperature rapidly goes to 102° or even higher, and areas of local pulmonary congestion are accurately made out. Such cases are amenable to judicious treatment, and in the course of ten days or two weeks very great temporary improvement will take place. I usually give very small, repeated doses of nux vomica and strophanthus in the beginning of these attacks. I insist

[1] British Medical Journal, August 16, 1884, p. 812.

upon rest in bed and frequent small quantities of liquid or easily digested food. Where there are cough and local signs of dry pleuritis a small fly-blister, though painful, is a sovereign remedy. Of course, the menstrual flow when excessive should be controlled with ergot or hot douches.

In some of these cases where there is also well-marked anæmia there is present at times and in a more or less continuous manner a small amount of albumin in the urine. The clinical examination of the urine is such that I have known patients of this sort to be told that they were suffering from nephritis, and it was essential for them to live during a long period upon a milk diet, and to reside in an equable, dry, and relatively mild climate. In these cases the albumin would at times disappear, but fatigue, indiscretions of food, temporary excitement would apparently bring back the albuminuria. I have no doubt the kidneys were affected with chronic congestion. I am also very confident that the hyperæmia was passive rather than active, and was, in reality, and mainly under the dependence of a weak heart, quite insufficient in its action to keep up a proper vascular tension in the renal arteries. Here, again, judicious cardiac treatment was essential at first. With the digitalis or strophanthus, however, I usually combine a small quantity of nitroglycerin, as I deem it very important to dilate the peripheral circulation and thus lessen the necessary work of the heart to become effective.

There is another type of woman, and she is usually thin and nervous about the time of the climacteric or past it. The menstrual flow if it still exists is slight. These patients may not be anæmic to any appreciable extent. They have frequently very imperfect digestive assimilation. They may have some dilatation of the stomach, and are frequently nauseated and unable to take even the simplest forms of food for a time without causing great and rapid gaseous distention, not only of the stomach but also of the bowels. The liver is inactive and the bowels are torpid. We can give few medicines by the mouth except stomachics and carminatives without making their condition worse. Although their heart is extremely feeble, so much so at times in fact that we dread almost to move or raise them to make a proper exploration of the chest, yet if we so much as try to use any medication by the mouth to strengthen heart action we shall almost surely bring on worse distress and perhaps

excessive nausea and repeated vomiting. I have been obliged to treat such a patient for days at a time with digitaline and strychnine hypodermatically, while inhalations of oxygen were frequently administered. Rectal alimentation with panopepton, peptonized milk, egg, brandy, and a little opium at times, took the place almost entirely of feeding by the mouth for several days. Where the repeated use of the hypodermatic syringe set up local irritation I was obliged to incorporate my cardiac stimulants with very small rectal enemata of water. Finally, after weeks of anxiety and constant nursing and unremitting attention, these women slowly regained their health and strength, and the heart became sufficiently strong to satisfy ordinary demands made upon it when the patient went about in a very limited measure. The urine never, upon repeated examinations, showed either albumin or sugar, but did show low specific gravity, deficient elimination of urea, and perhaps a few hyaline or granular casts. I could not positively affirm any general arteriofibrosis. I could and did strongly suspect its presence. The heart gave all the evidences of slight dilatation of the ventricular cavities, but at no time was there any manifest hypertrophy. In some patients there was rarely any cardiac murmur, and all I could detect, as a rule, was great feebleness of heart action without irregularity or intermissions. I have no doubt, for my part, that if these hearts were examined post-mortem they would show few or no changes other than those which follow. They would be soft and flabby. They would not retain their rounded, globular form, but would flatten on the table through partial collapse of the walls. There would be no valvular changes. The orifices might be slightly dilated. There would be, as stated already, slight enlargement of the cavities and thinning of the muscular walls. The color of the heart muscle would approximate that of the faded leaf; perhaps, usually, it would only be relatively pale and bloodless. The cavities would contain small, imperfectly formed post-mortem clots or liquid blood. Under the microscope we should find the striæ here and there imperfectly marked. There would possibly be some well-marked granular degeneration at times, and only very rarely the evidence of fatty degeneration. If the latter existed it would more likely be in patches in the capillary muscles, the septum, or the ventricular walls than generally diffused.

Unfortunately, these are at best clinical impressions rather than well-ascertained facts. And why? Simply because post-mortem examinations of these cases are not made. The patients do not die, in my experience, at least outside of hospitals. In hospitals, when they die, they have more advanced and graver phenomena of a similar condition, and then it is we can surely and positively affirm what our findings are.

In many instances I have had a report from the pathologist which in its main features was not unlike what I have attempted to describe. In this connection I would refer to a paper of Dr. Danforth, of extreme interest to me, read at the last meeting of this Association, on "Clinical Forms of the Uric-acid Diathesis." It seems to me that some of Dr. Danforth's cases may have been mainly instances of cardiac dilatation in which the renal manifestations were merely a resultant of a weak, feeble heart action. At all events, I have portrayed the other side of a clinical picture frequently encountered by myself. I do not wish to convey the impression that I have made a new discovery—such cases as mine are met with by all of you. They are also described more or less perfectly in almost every text-book of cardiac disorders of the last fifty years. Still, I am free to confess that I do not know precisely where you will find the clinical picture I have endeavored to delineate in quite the same terms.

I may be asked whether I do not find these cases also among men. Perhaps I do, but I do not recall them in such a vivid manner as to be able to portray them. The laboring man, even though he may never suffer from actual valvular disease, will undoubtedly have at times marked cardiac dilatation. But usually there is more or less hypertrophy combined with it, and, even though the heart has become very incompetent through structural weakness, there will be such considerable enlargement that we feel confident that the autopsy will show more or less thickening of heart walls. The same is true of old valvular disease accompanied with cardiac enlargement. It is equally true, as a rule, where the history shows that there has been a persistent and excessive alcoholic habit. This is true also, although in less degree, of the business or professional man affected with heart disease.

Extreme cases of heart dilatation and no hypertrophy are also met

with among men; but the minor degrees, those to which I have referred and tried to describe, are usually found among women. The intense heart failure, coming on rapidly, almost suddenly at times among men, and unquestionably due to very great cardiac dilatation, against which the heart is almost powerless to react, is sometimes seen after great excesses. These cases, as we all know, may be rapidly or suddenly fatal despite our most active means of resuscitation. Among these cases, however, are unquestionably some in which the physical signs of cardiac dilatation are impossible to determine accurately. I can, therefore, well understand that their existence should be denied. In place of such a diagnosis I cannot but substitute one of loss of nerve-power, either in the intracardiac ganglia or in the trunks of the vagi. To admit this would be perhaps also to acknowledge that the heart muscle was intact and the cavities of normal dimensions. Such a belief would be strengthened by those instances in which certain cardiac tonics, and especially digitalis, are of little apparent value, perhaps, indeed, directly injurious, and rest in bed and suitable liquid diet with alcoholic stimulants appear to be most useful.

Again, there are instances in which there is certainly no pronounced structural kidney change, where we watch closely the sequence of clinical phenomena. There is renal inadequacy only. The secretion of healthy urine, viz., of normal color, density, in sufficient quantity and without abnormal constituents, after a few days or weeks of rest, and when the patient is given easily assimilable food, returns and our temporary fears are allayed. In some cases I recognize a possible spasmodic condition of the peripheral vessels and especially of the kidneys. We have intimation of this by high pulse tension at times and the rapid good effects of repeated small doses of nitroglycerin. Occasionally I have seen cases in which the heart action was very feeble, without any accentuation of the aortic second sound, and where the radial pulse itself had no increased tension, and yet nitroglycerin was of undoubted service, for after its use the heart's action was notably improved, and the secretion of urine, from being almost colorless and even small in quantity, took on its normal appearance and character. No doubt the nitroglycerin acted as a direct heart tonic to the cardiac muscle itself; no doubt, also, it dilated the small vessels of the kidney, breaking up any spas-

modic condition that existed, and thus was of very great benefit to the patient. At all events, I have certainly seen nervousness, marked twitching of the muscles, apathy and somnolence—all symptoms, as I believe, indicating more or less so-called uræmic poisoning—disappear and the patient progressively improve until fairly good health and strength were established. Examples of this kind are not uncommon, I believe, as a resultant of what has appeared to be a grippal attack.

Through a contribution to the London *Lancet* in October, 1899, by A. E. Sansom, I am of the opinion that he, also, has seen cases not dissimilar. Cohnheim and Leyden have intimated that occasionally the underlying cause of uræmic symptoms is found in cardiac insufficiency. Hence the blood stagnates in the renal vessels. Clinical observations on contracted kidneys support this view, as does the use of cardiac stimulants for the relief of their manifestations.

From the point of view of prognosis the character of the pulse is often very important. When it is relatively weak and perhaps irregular the outlook becomes serious. Sir William Broadbent has pointed out the gravity of a pulse of low tension when accompanied with symptoms indicating possible cirrhosis of the kidney. I have frequently had occasion to make a similar observation. No doubt many of these cases, however, merely enter into the category of what Sir Andrew Clark has described as "renal inadequacy" accompanied with some degree of cardiac dilatation. These are a class of cases in which, although the kidney presented no alteration of structure, it was unable to produce a perfectly healthy urine. In these cases the urine is low in density and deficient in solid constituents, principally in urea and its congeners.[1]

I might lengthen this paper considerably. I prefer not to do so, as I very much desire a discussion from the members of the Association as to its value and truth.

[1] Albuminuria and Bright's Disease, by M. Tirard, London, 1899, p. 16.

A CASE OF ADDISON'S DISEASE, WITH MARKED EXACERBATIONS AND REMISSIONS IN THE EARLY PERIOD; TREATMENT BY SUPRARENAL EXTRACT FOR FIVE MONTHS, WITH GAIN IN WEIGHT AND STRENGTH, BUT WITH INCREASING PIGMENTATION.

By W. W. JOHNSTON, M.D.,
of Washington, D. C.

As I have had a case of Addison's disease under treatment with suprarenal extract for some months past, it may be of interest to present the patient and to read the record of his improvement. I have also collected all the cases reported as having been so treated.

F. B. C., a farmer, aged eighteen years, living in Oakton, Va., was admitted to the Columbian University Hospital, October 20, 1899.

History. His father and mother, five brothers, and two sisters were all living, and all have fair complexions.

But for an attack of measles at seven and whooping-cough at eleven, he has enjoyed excellent health, and was considered strong and large for his age.

In June, 1897, he first noticed that he could not stand as much hard work as usual without getting tired. This condition grew progressively worse, so that he had to give up work entirely during the following month, on account of great lassitude and loss of physical and mental energy. These symptoms were progressive with gradual loss of weight, and were accompanied by anorexia. In the month of August (1897) he began to improve slightly. The nausea and vomiting, which caused him the most distress, ceased, his appetite improved, and he gained in strength and weight to such an extent that he considered himself perfectly well, and resumed his former work about October 15th of the same year. During this attack his skin remained perfectly normal in color.

In July, 1898, one year after the first attack, the same symptoms recurred, but with increased severity, so that he was forced to go to bed. In addition to the symptoms previously mentioned he had persistent epistaxis and

marked pigmentation of the skin of a yellowish-brown hue. The discoloration was first seen on the hands and face, and gradually spread over the whole body, being more pronounced on exposed surfaces and in the folds of the skin. The following fall (1898) the discoloration became lighter, and he gained in strength and weight, but not sufficiently so as to resume his former work.

About July 1, 1899, he grew worse, and was so weak that one month later he had to abandon all work. The pigmentation of the skin became darker and more diffused than in the summer of 1898, with the same constitutional symptoms of the previous attacks. On account of weakness he remained in bed five weeks, and at the end of this time gradually improved, so that in three weeks more he began to go about, although he could not resume work.

He came to the University Hospital, October 20, 1899. On admission he weighed 121 pounds, had a bright and intelligent expression, and was fairly well nourished; the eyes were somewhat prominent and the sclerotics white; the skin was of a yellowish-brown color, except on the palms of the hands, soles of the feet, scalp, and under the nails, where it was of normal color. The pigmentation was deeper on the face, neck, back of the hands, the axillæ, groins, genital region, and the areolæ of the nipples. On the right side of the neck and on the chest were slightly elevated, mole-like spots, very dark brown in color, single and in groups, from the size of a pin-point to that of a large pin-head. These spots were also irregularly distributed over the trunk. In addition to these elevations there were small brown macules, the size of a penny, placed here and there over the trunk and limbs. The thyroid gland was slightly enlarged.

There was a line of light brown pigmentation at the junction of the mucous membrane of the lips with that of the mouth, more marked on the upper lip. Very small brownish spots were found upon the mucous membrane of the cheeks corresponding to points of pressure by the teeth. These were also irregularly scattered over the hard palate and uvula. The stomach and intestinal digestion were normal, although the appetite was not good. The bowels were regular, the stools normal in color and consistency. The spleen was normal in size, and the liver-dulness had a vertical depth of five inches.

The respiratory and genito-urinary systems and the urine were normal. The heart sounds were less distinct and the impulse was feeble. The blood was normal on examination.

Treatment and Progress. The patient was put to bed, given full diet, strychnine sulphate, gr. 1-30, after each meal, and a hot tub bath three times a week. Six days after admission the extract of suprarenal capsule, gr. iij, in tablet form, was given three times daily after meals. This dose was increased to nine grains, which has been continued up to the present time. From the beginning his appetite improved, he slept well, and while in bed did not complain of weakness. He tottered, however, when walking, and became a little dizzy in sitting up. As he gained in strength he sat up a

short time each day without fatigue, and on November 18th, about four weeks after entrance, he took a walk in the open air for half an hour. From this time he improved so rapidly that he sat up the greater part of each day and took a walk for an hour in the afternoon.

His weight on admission was 121 pounds; one week later he had lost three pounds eight ounces. About this time the tablets of suprarenal capsule were given, and the following week he gained three pounds, and continued to gain until November 28th, when he lost three ounces in four days. On December 1st he lost six ounces more, The next four days he was kept in bed, and on December 5th had gained two pounds fourteen ounces. His total gain for the seven weeks in the hospital was eleven pounds eleven ounces. During the whole course of his illness the temperature was subnormal.

He left the hospital December 8, 1899, weighing 132 pounds and 11 ounces, and feeling stronger than he had for some time past. The pigmentation of the skin had become a little lighter, due, probably, to the frequent bathing, and every symptom of physical weakness had disappeared.

On December 27th, nearly three weeks later, he had gained three pounds five ounces, and was steadily improving. The following week, however, he lost one pound. The next two weeks, although he felt perfectly well and seemed to be gaining strength, his weight fell three pounds. On February 2, 1900, he again reached his highest point, 136 pounds, gaining in seven days three pounds. From this time up to April 28th, the day he re-entered the hospital, he lost eight pounds seven ounces, although he felt well and much stronger than for over a year past.

Condition on Re-admission, April 28, 1900. Weight, 127 pounds 9 ounces, a gain of six pounds nine ounces since October 20, 1899, the day of his first admission, and a loss of five pounds two ounces since December 8, 1899, the day of his former discharge. During his second stay of twelve days in the hospital he gained eleven ounces.

He asserts that he feels perfectly well and much stronger than when first admitted. He has an intelligent, bright expression, is better nourished and more muscular than formerly, the eyes are not as prominent, and the sclerotics are still white. The skin is much darker in color except on the palms of the hands, the soles of the feet, scalp, behind the ears, and under the nails, where it is more normal in color. His nose is somewhat lighter and of a pinkish-brown hue. As before, the discoloration is deeper on the face, neck, back of hands, the axillæ, groins, genital regions, and the areolæ of the nipples. There are fewer slightly elevated pigment spots of dark-brown color on the neck and on the chest. All the cicatricial tissue is not pigmented. Here and there over the trunk can still be found a few brownish stains about the size of a penny. The thyroid gland is much larger.

The line of discoloration at the junction of the mucous membrane of the lips with that of the mouth is much darker in color, almost black, and more marked, as before, on the upper lip. There are large, brownish spots on the mucous membrane of the cheeks and hard palate. The stomach and intestinal digestion are normal, appetite excellent, and bowels regular.

TABLE OF CASES OF ADDISON'S DISEASE TREATED WITH SUPRARENAL EXTRACT.

Reporter.	Reference.	Dose, form, or method.	Length of treatment.	Effect on weight.	Effect on strength.	Result.
Blackader,	Montreal Medical Journ., vol. xxii.	Suprarenal gland.	4 wks.	Not noted.	Not noted.	Slight improvem't.
Maragliano,	Riforma Med., 1894, vol. iv.	Hypodermatic inject'n of suprarenal extract.	20 dys.	Increas'd.	Able to walk in 20 days.	Recovered.
Shoemaker, J. G.	Univ. Med. Mag., Philadelphia, 1894, vol. ii.	Hypodermatic inject'n of glycerite suprarenal extract of beef.	2 mos.	Not noted.	Marked improvement.	Improv'd
Oliver, T.	Internat. Clinics, Philadelphia, 1894, vol. ii.	Hypodermatic inject'n of suprarenal extract, 20 ♏ daily.	Not noted.	Slight gain.	Not noted.	Not noted.
Osler, Wm.	Inter. Med. Mag., Feb., 1896.	Fresh suprarenal extract of pigs, ʒss. three times daily.	May 16 to Sept. 10.	Gained 19 lbs.	Well-marked gain.	Recovered.
Bèclerè,	Thèse de Paris, 1896	Fresh extract given by mouth 1 month; subcutaneous injection of extract 3½ months.	4 mos. and 2 weeks.	Not noted.	Not noted.	Contin'd well for 1½ years.
Quine,	Journ. Amer. Med. Assoc., May 23, 1896	Suprarenal bodies by mouth.	Not noted.	Not improved.	No improvem't.	Death.
Bèclerè,	Journ. Méd. des Hôp., Feb. 25, 1898.	Suprarenal extract by mouth followed by subcutaneous inject'n of extract of gland.	Not noted.	Not noted.	Not noted.	Improv'd
Martin,	Bull. Medicine, 1898.	Subcutaneous inject'n of suprarenal extract.	Not noted.	Gained.	Gained.	Recovered.
Suckling,	Brit. Med. Journ., May 28, 1898.	Tablets of suprarenal extract gr. x daily, increased to 200 gr. daily.	1 year.	Gained.	Gained.	Recovered.
Foster, A.	London Lancet, 1899, vol. i.	Suprarenal extract 5 gr. by mouth.	Not noted.	Gain at first followed by loss.	Gained at first followed by rapid loss.	Death due to gastro-intestinal irritation.
Destat,	Lyon Méd., No. 48, 1898.	Injection of suprarenal extract.	Not noted.	Marked gain at first.	"	Death.
Hemet,	Thèse de Paris, 1897–1898.	By mouth.	Not noted.	Not noted.	Not noted.	Favorable.
Jones, E. L.,	Brit. Med. Journ., 1895, vol. ii.	Suprarenal extr. tablets by mouth.	1 mo.	Gained.	Gained.	Recovery.
Murrell,	London Lancet, Feb. 1, 1896.	Suprarenal extract in tablets.	6 wks.	None.	None.	Death.
Dyson,	Quart. Med. Journ., vol. iii. Part 1.	Tincture of suprarenal gland.	Few days.	None.	None.	Death.
Stewart, T. G.	20th Cent. Practice.	Adrenals raw, fed.	Not noted.	Not noted.	Not noted.	Not known.
Francis,	Brit. Med. Journ., May, 1896.	5 gr. tablets of dried gland 3 times daily.	10 mos.	Well-marked gain in weight.	Well marked, able to be about.	Died from relapse.
Stockman (1),	Edin. Med. Journ., Feb., 1897.	Six raw suprarenal glands from sheep daily.	20 mos.	Gained slightly after 2 mos. treatment.	Improv'd	Well for 20 mos.
(2),	Edin. Med. Journ., Feb., 1897.	" " " "	Not noted.	Not noted.	Not noted.	Death.
Bramwell,	Brit. Med. Journ., 1897, vol. i.	Tablets of suprarenal glands.	Not noted.	Not noted.	Improv'd	Improv'd
Robin, F.	These de Paris, 1897–1898.	Injection of suprarenal extract.	Not noted.	Gained.	Improv'd	G'd h'lth for 3 yrs.
Miliam,	Gould Year-book, 1898.	Hypodermatic inject'n of suprarenal extract.	Not noted.	Not noted.	Not noted.	Greatly improved
Turney (1),	Brit. Med. Journ., Jan., 1896.	Suprarenal extract, tablets, gr. iii, t. i. d.	Not noted.	Not noted.	Not noted.	Death.
(2),	Brit. Med. Journ., Jan., 1896.	Suprarenal extract, tablets, gr. iii, t. i. d.	Not noted.	Loss of weight	Loss.	Death.

Reporter.	Reference.	Dose, form, or method.	Length of treatment.	Effect on weight.	Effect on strength.	Result.
Oliver, G. (1),	Brit. Med. Journ., 1895, vol. ii.	Tablets gr. iii–v suprarenal extract.	12 mos.	Gain in weight.	Gain in strength.	Perfect recovery.
(2),	Brit. Med. Journ., 1895, vol. ii.	Dried extract gland in 3 and 5 gr. doses t. i. d.	Not noted.	Not noted.	Not noted.	Recovery.
Sansom,	Brit. Med. Journ., 1895, vol. ii.	Tablets suprarenal extract.	30 days.	Gained at first then lost weight rapidly	Not noted.	Unknown.
Althaus,	Brit. Med. Journ., 1896, vol. ii.	Suprarenal extract.	Not noted.	Gained at first then lost weight rapidly	Improv'd at first, became weaker.	Died.
Maragliano,	Gazette des Hôp., 1895, No. 7.	Glycerine extr. hypodermatically.	Not noted.	Not noted.	Not noted.	Not noted.
Stockton.	Med News, Nov. 16, 1895.	Two uncooked glands daily.	Not noted.	Gained.	Gained.	Recovery.
Schwab, L. W. (1) 2 brothers aged 55 & 57	Journ. Amer. Med. March, 1898.	Dried suprarenal extr. of sheep.	2 wks.	None.	No improvem't.	Unfavorable.
(2),	Journ. Amer. Med., March, 1898.	Dried suprarenal extr. of sheep	2 wks.	None.	No improvem't.	Unfavorable.
Ringer and Phear (1),	Brit. Med. Journ., Jan., 1896.	Suprarenal extract by mouth, 45 gr. daily, increased to 120.	6 wks.	Gained 4 weeks then lost rapidly	No improvem't.	Died end of six weeks.
" (2) (3) (4) (5) (6) (7) (8) (9)	Brit. Med. Journ., Jan., 1896.	Suprarenal extract by mouth, in various doses.	Not noted.	Not noted.	Not noted.	5 cases improved 2 not improved, 1 treatment stopped, 1 died.
Tonoli,	Gaz. Med., vol. xlv. p. 321.	Powdered adrenal tissue by mouth.	2 mos.	Gained.	Improved	Recovery.
Afflech,	London Lancet, 1898, vol. ii.	Tablets of suprarenal glands.	Not noted.	14 lbs.	Gained.	Much improved; died with tuberculosis.
Pickardt,	Med. Review, London, 1899, vol. ii.	Tablets of suprarenal glands.	Not noted.	Lost	Lost.	Not stated.
Berry,	London Lancet, 1898, vol. i.	Tablets of suprarenal gland gr. v, t. i. d., followed by glycerite of fresh gland of calf.	9 days.	None.	Not stated.	Sudden death, tuberculosis.
Bendu,	Med. News, New York, April, 1899.	Suprarenal extr. from calf, 20 gr. daily.	1 week	Slight	Not stated.	Death, tuberculosis.
Bate,	Amer. Pract. and News, Aug., 1899, vol. xxviii.	1/12 gr. sup. extract of sheep, t. i. d.	2 years.	Gained.	Gained.	Recovery, able to work.
Leibert,	Amer. Journ. Med. Sci., July, 1899.	Sup. extract tablets gr. v, t. i. d., increased to gr x, t. i. d.	1 year.	20 lbs.	Gained.	Improv'd
Leibert,	Amer. Journ. Med. Sci., July, 1899.	5 gr. of extr. administered by rectum t. i. d., then by mouth same dose.	4 wks.	Slight.	Slight.	Improv'd

Total number of cases	50
Recovered	10
Improved	16
Not improved	3
Died	13
Result not given	8

The heart sounds are strong and slightly accentuated, but of normal rhythm. The blood examination shows no change from health.

He is still taking the tablets of the extract of suprarenal capsule, gr. ix, three times daily after meals; is allowed to sit up as long as desired daily, and gets a hot tub bath three times a week.

The features of this case which are of interest are the very acute prostration during the earliest period, three years ago, the gain in strength during the winter following, with a return of more marked asthenia during the second summer, the marked improvement under rest, with the gain in strength and flesh for five months while taking suprarenal extract.

WOULD IT NOT BE A GAIN TO BOTH PATHOLOGY AND PRACTICE IF A DIRECT INTERACTION BETWEEN THE MORBIFIC AGENT (NOXA) AND THE REPARATIVE EFFORT WERE RECOGNIZED AND THE CONCEPTION OF AN INTERMEDIATE, SO-CALLED INFLAMMATORY PROCESS ABANDONED?

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Since the dawn of medical science inflammation has been the corner-stone of pathology. Of late years, however, its influence has waned. It has been shorn of its attributes one after another, until the question now fairly arises whether a valid title to recognition any longer exists in its behalf.

Originally inflammation was held to be present wherever the four cardinal symptoms were observed—redness, swelling, heat, and pain. It is not likely that the term was first suggested by cases involving obvious traumatism, but rather by cases of apparently spontaneous origin.

If, for example, a sliver of wood is thrust into the finger and left there, we have as a result redness, swelling, heat, and pain. These, however, would be readily referred to the presence of the foreign body, and if they were never present collectively, except under this or similar conditions, no one would ever have thought of inventing a special term to express their concurrence. The idea would have been simply that of an injurious influence acting directly upon the tissues. But inasmuch as the same collocation of symptoms is observed at times, in the absence of obvious traumatism and with no apparent cause, it was natural to assume that the tissues were

subject to invasion by a morbid state, condition, or process acting independently and constituting a new force or agency to be reckoned with by itself. As the practice of post-mortem examinations came more into vogue this idea received support from finding that internal organs that had been the seat of pain during life were often found swollen and red after death. The symptom of heat was, of course, not determined; but its presence during life might well be assumed, especially if fever had been observed. Thus the conception of inflammation as a condition expressed by these four cardinal symptoms became firmly rooted in the medical mind. Later, the term was extended to cases in which the products of the so-called inflammatory process were found upon the surfaces of internal membranes or enclosed in cavities. To so extend the idea, however, it was necessary to drop some of the characteristics of inflammation, as up to that time they had been accepted. Thus pain was often absent and swelling could not be demonstrated in every case; but the surface was red, and pus or lymph adhered to it, and this was taken to establish the identity of the action with that which gave rise to the characteristic symptoms already enumerated.

Gradually it came about that nearly every change from normal structure was ascribed to the action of this agent; but, one after another, all the original marks of inflammation had to be given up as essential to its conception except so much of swelling as is due to exudation. This is now all that is insisted upon to identify a process as inflammatory—all that there is in common in conditions that are as different from each other as it is possible to imagine.

But in doing away with all but this one test by which inflammation is to be recognized the difficulty of defining the term is immensely increased. This difficulty is inevitable so long as we insist upon the idea that a new action is "set up" by some exciting cause, and that once initiated this new action goes on independently and works out results of its own motion. The trouble lies in ascribing to an immaterial conception the power of acting upon matter and effecting physical changes in it. We are warned that inflammation is not a state or condition, but a *process*. Now, a process is simply a going forward, and cannot be conceived of apart from the thing that goes forward; neither can it be credited with possessing any form of energy. The morbific agent (noxa), whether it be an injury

or an infecting microbe, exerts a direct destructive power derived from material sources. The tissues have a defensive and reparative power derived from the living substance of which they are composed. "Inflammation" as a "process" has no material source of energy.

It is an error, therefore, to attach to it any idea of activity. The noxa may be active, the tissues may be active, but the "inflammation" never. It is simply a name, not a force. It can *do* nothing. The collision of two armies is called a battle, but the battle is not an entity apart from the armies. Much less can it join forces with one of them and help on the fight against the other. Yet this is what inflammation is supposed to do when it is credited at one time with opposing the noxa and helping forward the reparative effort, and at another time with "attacking" and "destroying" the tissues.

Following on in this line we cannot fail to see that the energy that initiates the "inflammation" is the energy that maintains the "inflammation;" that the latter has no momentum of its own; that it can go no further than the noxa carries it. This does not mean that it is only another name for the noxa. On the contrary, it is the trend of the newest pathology to identify "inflammation" with repair.

The same power which, working in the embryo, evolves a living being, continues its operation thereafter as a reparative force. In health its function is only to supply the natural waste, and until maturity to provide for growth; but disease or injury demands a further activity. The same prescient adaptation of means to a predetermined end that makes of one embryonic material a brain here and an eye there, with heart and liver, arms and legs, each in its proper place, lays out a plan of repair based upon the nature and extent of the damage to be repaired. If, for example, a foreign body is lodged in the tissues, the reparative effort will differ in accordance with the nature of that body and the degree of irritation which its presence occasions. If it is smooth, compact, and not liable to corrosion, the reparative action will be limited to enclosing it in a capsule, where it will remain harmless. If, on the other hand, it is jagged and porous, or if it is of a material easily corroded, an effort will be made to expel it. This effort will include an effusion of leucocytes, which will detach the foreign body from the tissues with

which it is entangled and surround it with fluid, which fluid will ultimately work its way to the surface, and through the opening thus made the intruding substance will be thrown out. Now all this is nothing more than a reparative effort on the part of the tissues—a modified expression of the vital energy by which they were originally constructed. It is in no proper sense a new force projected into the field to work at haphazard, a disturbing influence, an enemy to be dreaded, a foe to be "combated," a disease to be "treated." Yet as such and under the name of "inflammation" it is too commonly considered.

But the case is somewhat different when in place of a lesion accomplished at a single stroke we have a continuous morbific action working upon the tissues. The process then is twofold, consisting of a destructive action on the one hand and the reparative effort on the other. Such a condition obtains when, for example, the part is infected with pathogenic bacteria. Here a continuous assault upon the tissues is maintained, to which the reparative process opposes such resistance as it can, while endeavoring at the same time to limit the field of action by erecting barriers to fence it off. It is a fair grapple between two contending forces, and there is no room for a third. It does not excite an inflammation and then leave the inflammation to make the attack. Yet this is precisely what it is credited with doing, as is witnessed by the constant use of such terms as "infective peritonitis," "pneumococcic pericarditis," "malignant endocarditis," etc. It seems to be assumed that the microbe, transmuting itself from a material entity into an immaterial process, acquires thereby an extraordinary potency. It has been suggested, for instance, that "the infecting microbes have not that quantitative relationship to the effect which, in the physical sense, true causes must always bear," but that they only serve to set in motion a new mode of action which is the real cause of the morbid phenomena. They are the spark that lights the gunpowder, while it is the potential energy hidden in the powder that when made active causes the explosion.

But the comparison, to be just, should require a continued spark setting off a continued supply of gunpowder, even as a continued succession of microbes is required to keep up a continued "inflammation." Withdraw the microbes, and we all know how immediately

the process ceases. The tubercle bacillus is not tubercle, it is true; but its continued, not alone its initial, presence is necessary for the persistence of tuberculosis. Also, gunpowder explodes in precisely the same way, no matter whether ignited by a match, a friction primer, or an electric spark, and the igniting agent disappears from the scene. Not so, however, in an "inflammation." The explosion constantly and persistently betrays the character of the spark, and if we want to designate more accurately what kind of an explosion we are dealing with we employ an adjective that designates the character of the spark. We speak of "streptococcus" inflammation, "pneumococcus" inflammation, etc., and we recognize that the adjective is the more important part of the phrase. The inflammation is so thin a veil that the cause shows through at every point.

As for the power of the noxa, in and for itself, to deliver an effective attack upon the tissues and to call forth their protective and reparative energies, there can be no question, of course, as regards all the various forms of trauma in the old sense of the term. Obviously, in mechanical, chemical, and thermic injuries the result upon the tissues will be exactly proportioned to the degree of the noxious energy. The same is true in those cases in which the noxa is such by virtue of a peculiar vital relation to the tissues. Thus, certain substances which would produce no change whatever in tissues deprived of their vitality, cause exceedingly active changes in living tissue, and this, too, in the absence of any microbic action. Among these are cantharides, mustard, turpentine, etc. But it is also evident that certain microbes which we call pathogenic have a destructive power, either in themselves or in the toxins they produce, which may be sufficient to devitalize the tissues upon which they act. The coagulation necrosis effected by the Klebs-Loeffler bacillus is an instance in point.

Less virulent organisms may not cause the actual death of the tissue, but they may so impair the structure as to necessitate more or less of renewal. Their persistence in the tissue will then be the source of continued unusual vascular and cell activity, not a new kind of energy, but an increase of that previously existing and tending to ultimate repair.

In this repair of tissues, as in the repair of a building, an accumulation of material is necessary. This material is brought by the

blood, and the increased demand requires enlarged vessels; hence hyperæmia, with its accompanying heat and redness. The material is for the most part required for use outside the vessels; hence effusion of serum and diapedesis of cell-elements, and this in turn produces swelling. The pressure upon nerve-fibres causes pain.

Thus we have the four cardinal symptoms of "inflammation" as the natural consequence of an effort toward repair, and without the necessity of invoking the aid of any other "process."

As to certain incidents which may or may not occur in the course of these changes, such, for example, as suppuration and fibrosis, they are entitled to be considered as independent phenomena, like the sugar formation in diabetes, rather than to be regarded as manifestations of a dominating process such as inflammation is assumed to be. Indeed, the multifarious and dissimilar things that are supposed to follow in the train of inflammation defy all efforts to trace a family likeness among them. What two things, for instance, could be more unlike than suppuration of the middle ear and sclerosis of the tympanum? Yet they are bracketed together under the title of otitis media.

As a matter of fact, we find the most recent American authorities are by no means agreed as to what manifestations are to be included in the inflammatory process and what are to be left without the pale. Thus, in Park's *Surgery by American Authors*[1] the term inflammation is restricted to those disturbances which are produced by bacteria themselves or by their toxins, and which tend toward pus formation. Nancrede holds a similar view, and entitles one of his lectures *Inflammation a True Microbic Process* (p. 65).

Indeed, most surgical writers are inclined to exclude fibrous hyperplasia entirely from the idea of inflammation, in opposition to the physicians who find in it a favorite form of "itis." If the surgeons would go a step further and accept pyogenesis as a tub standing on its own bottom, they would be rid at once of the incubus of inflammation under which their medical brethren are weighed down. How great is this incubus will be seen when the difficulties in the way of arriving at a definition are appreciated. These difficulties are so great that some writers decline the task, and those who accept

[1] American Journal of the Medical Sciences, p. 335.

it speak in hesitating and uncertain terms. We have in "inflammation" an inheritance that plagues us, but we have not quite the courage to throw it off, and meantime we have to apologize for it as best we can. To my mind it seems clear that in "inflammation" the tissues behave thus and so not because they are attacked by an indefinite, undescribable, *immaterial* process, but because they are attacked by a definite, demonstrable *material* noxa. If we inject sterilized oil of turpentine into the cellular tissues the place becomes red, hot, swollen, and painful, not because it is the seat of "inflammation," but because it is the seat of so and so many drops of oleum terebinthinæ. In scarlatina the structure of the kidney undergoes changes, not because it is "inflamed," but because its elements are saturated with a *material* irritant poison. Peritoneal infection kills the patient not because an "inflammatory process" has been "lighted up" in his peritoneum, but because his peritoneum is permeated by myriads of bacteria, whose toxins, poisoning a vast aggregate of nerve-endings, inflict a corresponding shock. Twisting an ankle produces immediate tumefaction, accompanied by intense pain, heat, and redness, not because it initiates a new *process*, but because of the mechanical injury inflicted upon the structure of the joint, and the afflux of blood called for as the first step toward repair.

At this point I shall be met by the statement that I am seeking to establish what is already granted, and that no authority accords to inflammation the position of a distinct and separate pathological energy. Perhaps not in stated terms, but in our text-books there is a variance between the definition of the term and the treatment of the subject. The term may be defined into thin air, as merely another name for something else, but the subject is treated as systematically and as exhaustively as typhoid fever or measles or any other pathological or nosological entity. Its etiology, symptoms, progress, and treatment are duly set forth, and in every respect it takes the position of a disease; in fact, the most important of all diseases, or, as a very recent authority denominates it, "the dominant process in disease." So long as this continues to be the case the practical objection remains, and the doctrine of inflammation continues to be, as I think, an obstruction to the progress of medical science—that is, something built up across its path.

I feel assured, at least, that if the whole field of pathology were investigated anew, without any historical bias and in the light of modern bacteriology, the idea of inflammation would never once occur to any investigator. And even now, with our minds saturated with the old habits of thought, I am convinced that when we shall have exhausted the study of the various forms of noxæ and their modes of action on the one hand, and on the other the defensive and reparative action of the tissues, we shall find that the ground has been completely covered, and no place has been left for the study of "inflammation." Led by this conviction, I feel constrained, at whatever risk of being deemed presumptuous, to ask the question that forms the title of this paper, and to answer it as to my own belief, affirmatively. Accordingly I venture the proposition that the entire doctrine of "inflammation" should be abandoned, and that the phenomena ascribed to this process should be assigned to new relations in accordance with recent advances in pathology, and especially in bacteriology—advances that have rendered obsolete a conception handed down to us from remote ages.

In the matter of nomenclature this proposal would involve, of course, doing away with the termination "itis." As most of the phenomena heretofore included under the term "inflammation" are manifestations of the local action excited by a micro-organism or by a poison circulating in the blood, I would propose that such action be expressed by a termination to be affixed to the name of the organism or poison, if the same can be determined, or to the organ or part affected in case the particular infecting organism or poison is not identified. We have a universally accepted precedent for the first named use in the case of *tuberculosis*. I would propose that we extend the use of this termination to the action of other organisms, and express by *streptocosis* an infection by the streptococcus; by *staphylocosis* an infection by the staphylococcus; by *gonocosis* an infection by the gonococcus, and so on, using a localizing adjective to denote the seat of the affection. Infection by an undetermined organism would be *microbosis* or *bacteriosis* as a general term, or it would be expressed by adding the termination to the name of the part in the same way as "itis" is now employed.

Under this nomenclature *pericardosis* would denote simply infection of the pericardium; *pericardial pneumocosis*, infection of the

pericardium by pneumococci We should have, also, *scarlatinosis* (renal, glandular), *rheumatosis* (articular, endocardial), etc., expressing the local action of a poison in the blood.

If a general name is demanded as a substitute for "inflammation," I would say that no one word ought to be made to include all the heterogeneous, unrelated processes and conditions which have been comprised under that term. At least three words would be required to express different kinds of noxæ acting in different ways and leading to essentially different results.

These might be *traumosis*, to include wounds and injuries; *toxosis*, to include the local action of poisons in the blood; and *bacteriosis*, to include the action of micro-organisms. These would comprise the processes and conditions that have a fair claim to be recognized as inflammatory under the present nomenclature. There are others, especially among the very chronic tissue changes, whose claims are doubtful, but which are sufficiently described already by names not ending in "itis."

The present limited use of the termination "osis" in such words as fibrosis, cytosis, etc., and in designating certain skin affections, would cause no embarrassment, as the meaning would always be made plain by the context.

But this is not merely a matter of words and names and definitions; it is a matter of great practical importance as well. For so long as inflammation presents itself before us as the object of our therapeutic efforts, something to be "combated" or "controlled" or "subdued," so long we are tempted to look away from the continuously acting morbific agent, and at the same time to ignore the effort that the tissues are making for their own defence and repair. In striking at the *ignis fatuus* of inflammation we overlook our real enemy and are liable to injure our friend.

For example, if we treat the *inflammation* in a furuncle by application of cold we may succeed for a time in diminishing the swelling, redness, heat, and pain; but the noxa, in the form of bacteria, will still be there, and we shall certainly have to deal with it in the end. We have only deferred the evil day and added to the sum total of our patient's suffering.

Or, again, if bacteria are at work in the appendix vermiformis, and we are very successful in "combating the inflammation" by

our local and general treatment, we may succeed in preventing the effusion of lymph that would have walled in the infected area, and be rewarded by seeing our real enemy in possession of the entire field of the peritoneum.

Or, once more, if we have a multitude of colonies of pneumococci growing in the exudate which is occupying the air-cells of a portion of lung, and we seek to "control the inflammation" ("pneumonitis") by means of "arterial sedatives," such as antimony and veratrum viride, we may find a little later that we have only diminished the power so sorely needed to propel the blood through the obstructed lesser circulation, and added to the danger that our patient will succumb to failure of the right heart.

And, as a last illustration, if through fear of "feeding the inflammation" we are led to starve our patient, we shall in many cases deprive the tissues of just the nourishment required to enable them to resist the morbific influence against which they are contending. In this connection how eloquent is the hackneyed prescription of "cod-liver oil and iron" as a sequel to the "antiphlogistic treatment" of half a century ago. And here I would remark that the task of the hour seems to be to square our theory with the lessons in practice which we have learned empirically.

But it is not to treatment alone that advantage would come from doing away with the idea of inflammation. It would lead to more exact diagnosis. As it is now, the average diagnosis is supplied by merely adding the termination "itis" to the name of the organ or part that has, or is supposed to have, something or other the matter with it. No attempt is made to determine, or at least to designate, the morbific agent underlying the phenomena. The "itis" forms a pit into which anything and everything are thrown, from hyperplasia of the cardiac valves to empyema; from thickened ear-drum to hip-joint disease; from in-growing toe-nail to atrophy of the renal cortex; from housemaid's knee to "myocarditis;" from ulcer of the cornea to dysentery; and from "pink-eye" to "milk-leg." The plan proposed would at least demand some effort to discriminate between conditions as wide asunder as the poles. The use of the less exact designation would be a confession of failure to arrive at the one more precise and a self-rebuke for indolent and slovenly methods.

The demand of the day is for absolute, uncompromising truth in everything relating to science. In literature there is ample play for the imagination, but here precision of thought and of language is exacted. The physicist would not for a moment tolerate the idea of a material effect being the product of an immaterial cause. The doctrine of the conservation of forces presupposes a material basis underlying every manifestation of energy. Why should we continue to employ language that implies a different law or indifference to law in medicine?

A STUDY OF TWENTY-FOUR CASES OF TYPHOID FEVER WITH SYMPTOMS OF PERITONEAL INFECTION. LAPAROTOMY.

SUMMARY.—SEVENTEEN CASES OF PERFORATION OF INTESTINE; TWO CASES OF PRE-PERFORATIVE NECROTIC AREAS; ONE CASE OF RUPTURED MESENTERIC GLAND; THREE CASES CAUSE OF SYMPTOMS UNDETERMINED, DIAGNOSIS NOT CONFIRMED.

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THE whole number of cases studied by this committee is 27, all coming in the years between 1895 and 1900: 9 cases from the Massachusetts General Hospital; 16 cases from the Boston City Hospital; 1 case from St. Elizabeth's Hospital, and 1 case from the Boston Children's Hospital.

In the year 1895 there are 3 cases, but only one of them will bear analysis as a case of genuine typhoid fever; 1 case in 1896, 4 cases in 1897, 5 cases in 1898, and 14 cases in 1899.

This is a striking illustration of the increase in the operative tendency. The data from which this analytical report has been made are the complete medical, surgical, and post-mortem records of the several hospitals, together with the summarized statements and opinions sent in by the physicians and surgeons in attendance. From this available material a concise view of each case has been made with reference to all the important points bearing in any way on the diagnosis and treatment of peritoneal infection in typhoid fever.

The committee would deprecate its critical comments of to-day being interpreted as fault-finding with the practice of earlier years; neither does the committee forget that the ideal is not always, or under all conditions, to be realized in practice. Doubtless a nearer approach to the ideal should be aimed at and would now be possible than is found in most of the cases here reported. And the committee is still further quite aware that the ideal itself—for example, in regard to such a matter as the value and application of the white blood-count—is subject to further changes; the value of pain as a warning symptom also merits further study.

Of the 27 cases, A, B, and C must be thrown out of our consideration, because of no proof that they were genuine cases of typhoid. Cases B and C were both cases of advanced general peritonitis when first seen, and in both of them there was no proof that typhoid was the origin of the peritonitis.

Case A was brought to the City Hospital in a moribund condition, and showed general peritonitis at the operation. Cultures from the interior of the gall-bladder showed the presence of the bacillus typhosus. This, however, cannot be accepted as conclusive proof that the case was one of typhoid peritonitis. Cultures from the peritoneal fluid showed only the staphylococcus albus. It is an accepted fact that typhoid bacilli can and do remain active in the gall-bladder for months and years after an attack of typhoid fever. For example, Miller[1] has reported a case in which the bacillus typhosus was found in the gall-bladder seven years after an attack of typhoid fever. There is no proof, therefore, that the peritonitis in Case A might not have been of other origin than typhoid fever, and, therefore, it cannot be included in our list of cases for study. This series, then, embraces 24 cases, which are all undeniable cases of typhoid; there can be no controversy on this point.

Eighteen cases had a positive Widal serum reaction in addition to the evidence furnished by the clinical course of the case and the positive pathological evidence furnished by the operation or post-mortem examination. In 3 cases the Widal test was not made; in 3 cases the Widal test was negative. Two of the cases in which it

[1] Johns Hopkins Hospital Bulletin, May, 1898.

was not made occurred in the years 1895 and 1896, a period of time before the use of the test.

Of the 6 cases in which the Widal test was not made or was negative there can be no doubt of the diagnosis of typhoid, because of the findings at the operation or the post-mortem which fully corroborated the clinical diagnosis. In 2 of the cases in which the Widal test was not made the diazo test was positive.

All of the 24 cases had symptoms upon which a diagnosis of intestinal perforation was made and for which an operation was performed.

Three of the cases (22, 23, and 24) presented symptoms strongly suggestive of intra-abdominal infection, and accordingly were operated upon with a diagnosis of intestinal perforation, but at the operation no positive cause for the symptoms was found. Two cases recovered from this exploratory operation and one died. These cases are of the greatest importance from the diagnostic point of view, and will be considered carefully when the subject of "Symptoms and Diagnosis" is taken up.

Case 19 had characteristic symptoms of acute sudden peritoneal infection, and operation discovered a general septic peritonitis, but did not determine the cause; therefore this case should not be classed with those in which the cause of the peritonitis is certain, although it certainly seems rational, on considering the history and the symptoms and the fact that several different thin places in the intestinal wall were found at operation, to consider it a case of perforation.

In Cases 2 and 16 the classic severe symptoms of perforation were simulated, but operation discovered the cause of the symptoms to be a general septic peritonitis originating in damaged and necrosed areas of peritoneum over the bases of one or more typhoid ulcers. These cases might be called cases of progressive peritoneal infection from threatened perforation.

In Case 21 the symptoms amply justified the diagnosis of intestinal perforation, but operation proved that the symptoms, which were identical with the usually accepted symptoms of perforation of the bowel, were due to a general septic peritonitis arising from a ruptured mesenteric gland.

So that out of the 24 cases of true typhoid only 17 were cases

of peritoneal infection from actual perforation of the intestinal wall.

Two cases were of general infection from threatened perforations or areas of necrotic peritoneum; 1 case of general infection from a ruptured mesenteric gland; 1 case of general infection from an unknown cause, presumably intestinal perforation; 3 cases had no certain cause for the symptoms which demanded operative interference.

Since it will be shown that in many cases no differentiation between the usually accepted symptoms of actual perforation and the symptoms of general septic peritonitis can be made, this series of 24 cases gives us, for further study, 21 cases of grave peritoneal infection in typhoid fever and 3 cases of mistaken diagnosis, but with symptoms of peritoneal infection.

Diagnostically and from the point of view of treatment all of these cases should go in under the head of acute peritoneal infection in the course of typhoid fever. It may be well, however, to analyze the two groups of cases separately, dividing the perforations from the other cases.

Of the 24 cases presenting acute abdominal symptoms, with or without discoverable cause, 18 were males and 6 were females. Of the 18 males 15 were under thirty years; 1 was forty-five years; 1 was thirty-eight years; 1 was thirty-two years; 14 cases were between the years of nineteen and thirty, and 1 case was sixteen years. Of the females, 6 in number, 4 were between twenty and twenty-six years, 1 was forty years, and 1 was sixteen years.

The total number of cases shows, therefore, that acute abdominal infection occurs most often in young adults between the ages of eighteen and thirty years; that it is most frequent in men; that it is rare in children. It is noteworthy that two of the cases presenting acute abdominal symptoms without discoverable cause occurred in young women, aged twenty and sixteen years respectively.

These facts in regard to age and sex are in general accord with the investigations of Dr. R. H. Fitz and others, although the percentage of those under thirty years of age happens to be somewhat larger than in Dr. Fitz's tables.[1]

[1] Transactions of the Association of American Physicians, vol. vi. p. 200.

As to the question of typhoid perforation in children under twelve years of age, we have been able to find but 4 cases of operation for perforation in children under that age in all the cases reported in literature.

Cushing:[1] Boy, nine years old, on which case three laparotomies were done; the case recovered. Three cases are given in Keen's[2] tables of cases of operation for typhoid perforation.

All the cases but one were white in color. This proportion of blacks to whites would very likely be different in other parts of the country, where the proportion of the colored population to the white is greater.

In 18 of the 24 cases the clinical nature and course of the typhoid *was mild*, and in 15 of these 18 mild cases perforation or general septic peritonitis was present. The 3 cases which presented symptoms without certain cause were mild cases.

One case, No. 17, was a "walking typhoid;" 6 cases, Nos. 2, 6, 8, 12, 14, and, 20 were *severely sick* typhoids. All of these 6 cases had general septic peritonitis from actual or threatened perforation, and all died.

These facts are in accord with the hitherto accepted knowledge that intestinal perforation in typhoid frequently occurs in those cases of a mild type, or, in other words, there is no relation between the severity of the course of the fever and the likelihood of intestinal perforation.

The difficulty of the diagnosis of the peritoneal infection in cases of the severe type will be touched upon later.

The sudden fulminating symptoms in the severely sick cases will be found in the majority of instances to be due to a general septic peritonitis, which was often unsuspected and had slowly progressed. On the other hand, a sudden, acute onset in the mild type more often meant sudden intestinal perforation with extravasation. In certain of the severely sick cases in this series it would seem as if a diagnosis of the onset of the peritoneal infection was practically impossible.

The organic complications were very few: 3 cases had mitral regurgitation amply compensated; 1 case in which operation dis-

[1] Johns Hopkins Hospital Bulletin, 1898.
[2] Surgical Complications and Sequels of Typhoid Fever.

covered no cause for the symptoms had an especially feeble heart, with mitral regurgitation, yet this case recovered from the exploration; in 9 cases intestinal hemorrhages are noted; in 2 cases it occurred three weeks before the severe symptoms of perforation appeared; in 2 cases it occurred forty-eight hours before the severe abdominal symptoms, but there was a distinctly comfortable period between the occurrence of these hemorrhages and the sudden onset of abdominal pain. In 3 cases intestinal hemorrhages preceded and coincided with the beginning of peritoneal infection. Case 19 had daily intestinal hemorrhages for three days before sudden abdominal symptoms. Case 12 had a severe hemorrhage five days before the symptoms for which operation was done; but this case was so sick and stupid as to justify the supposition that perforation probably took place long before the foul and evidently long-established general peritonitis was diagnosed. Case 6 had two severe hemorrhages just preceding and coincident with the perforation. In 2 cases intestinal hemorrhages are noted after the operation. In Case 1 a severe hemorrhage five days after the operation was undoubtedly the cause of death.

Intestinal hemorrhage, inasmuch as it must come through extensive ulceration of the intestinal wall, and since this may mean proximity to the peritoneal coat of the intestine, must be to a large extent a danger signal of perforation. The occurrence of intestinal hemorrhages, therefore, should properly demand a close watch for the symptoms of beginning peritoneal infection, frequent examination of the abdomen to detect tenderness or abnormal rigidity and muscular spasm, associated with frequent leucocyte counts. The occurrence of acute abdominal pain following and coincident with intestinal hemorrhage should lead to the suspicion of peritoneal infection.

The Week in the Disease in which Peritoneal Infection Took Place.

Of the cases in which perforation and general peritonitis existed the acute abdominal symptoms appeared at the following times: In 5 cases at the end of the second or first of the third week; 8 cases at the end of the third week; 1 case during the fourth week; 4 cases during the fifth week; 1 case during the sixth week; 1 case

during the ninth week; 1 case during the eleventh week in a relapse.

Of the cases operated upon under a mistaken diagnosis 1 was in the fourth week, 1 in the fifth week, and 1 in the sixth week. The diagnostic symptoms of intestinal perforation in typhoid as they are usually understood, namely, sudden abdominal pain, fall of temperature, collapse, general abdominal rigidity and tenderness, with or without vomiting, anxious facies coming on without warning, do not present themselves as a complete picture in any one of this series of cases. The majority of the cases show records of definite warning symptoms, or, in other words, present evidences of a gradual onset of peritoneal infection.

It is, in fact, rational to conclude from a study of the symptoms in these cases, together with the findings at operation, that the severe symptoms corresponding to the ordinary text-book picture of intestinal perforation in typhoid were, in the majority of cases, caused by the general septic peritonitis resulting from a perforation or a threatened perforation, the occurrence of which (the perforation or local area of infection) was indicated more or less plainly by symptoms of less severity which antedated the severe or so-called diagnostic symptoms by a definite number of hours.

If it is one thing to operate for intestinal perforation, and a decidedly different thing to operate for a septic peritonitis resulting from a perforation, the fact should be thoroughly understood that the severe and usual diagnostic symptoms in this class of cases meant that septic peritonitis had already existed for some time, and that the perforation took place at a previous time and was evidenced by milder and more localized symptoms. It is a fact that in the majority of these cases definite premonitory symptoms are recorded at a time more or less remote from the severe symptoms which first led to the diagnosis, and for which the physician called the surgeon in consultation.

Seven cases of the 21 in which operation found cause for the symptoms, namely, Nos. 1 to 7 inclusive, presented a sudden, acute picture of grave abdominal infection without *any* premonitory symptoms. Of these 7 cases, 5 (Nos. 1, 3, 4, 5, and 7) were mild typhoids, whose general and mental condition was favorable to the noting of abdominal pain. Two cases (Nos. 2 and 6) were very

sick, stupid, and semiconscious; a class of cases in which the occurrence of considerable localized abdominal pain might not be noted. In Case 2 the symptoms, sudden though they were, were due to a general peritonitis from the damaged peritoneum over the base of one or more ulcers, and not due to a sudden perforation. In Case 6 the sudden symptoms were caused by the presence of a general peritonitis which had extended from a localized abscess originating from the intestinal perforation, which at its appearance had given no symptoms, so that of the 7 cases which present fulminating symptoms and which most closely conformed to the hitherto established idea of the symptoms of intestinal perforation only 5 proved to be due to *actual sudden perforation*, while 1 was not a case of perforation at all, and in the other the perforation and progress of the localized peritonitis with abscess formation did not cause any symptoms.

The sudden onset in these 7 cases presents a different picture in the 5 cases in which the symptoms were proved to be due to actual perforation. In these cases we have the symptoms of sudden severe pain coming on without warning, more or less localized in the right iliac region, accompanied by localized muscle spasm and tenderness with the varying amount of shock. In the two cases in which the symptoms were due to general peritonitis we have a picture suggesting general peritonitis, marked collapse, great distention, and general tenderness and rigidity. It might be concluded from a study of these 7 cases that in mild typhoids the appearance of sudden severe abdominal symptoms without any previous abdominal pain or tenderness may most often mean sudden intestinal perforation with extravasation into the general peritoneal cavity, and that the symptoms may vary, the chief symptoms being sudden pain, tenderness, and muscular spasm localized, attended with more or less marked shock; but in very sick and lethargic cases the appearance of severe abdominal symptoms without warning most often means the presence of general septic peritonitis originating in some one of the possible sources of peritonitis in typhoid, the gradual onset of which it has been impossible to diagnose because of the sick and stupid condition of the patient.

It has been stated that in the above 7 cases there were no warning symptoms. By this is meant direct abdominal symptoms—

pain, tenderness, and muscular spasm. It should be stated, for the sake of completeness, that 3 cases had one or more intestinal hemorrhages on the two days preceding the acute abdominal symptoms. One case had several hard chills without hemorrhage during the twenty-four hours preceding the onset of the peritoneal symptoms. The occurrence of chills as a symptom of peritoneal infection in typhoid is probably rare. It can only be a symptom leading to suspicion of infection when it is unassociated with hemorrhage.

J. F. R. Gairdner[1] states that rigor as an initial symptom of peritoneal infection in typhoid is uncommon. He noted it in only 2 cases out of 47 studied by him. It is noteworthy that in one of his cases and in the case of Jenner the peritonitis ushered in by rigors was due to the rupture of a softened mesenteric gland. In Case 21, the only case of our series of peritonitis from the same cause, no chill occurred. In the absence of intestinal hemorrhage to account for rigors it might not be irrational to suppose that it might occasionally be present in the early stages of peritoneal infection.

In those 3 cases in which no cause for the symptoms was found at operation the onset of the same was gradual. These cases will be referred to again in the subject headed "Symptoms and Diagnosis."

We have 14 cases, namely: Cases 8 to 21 inclusive, with more or less gradual onset of the abdominal symptoms. Eleven of these are cases of intestinal perforation and resultant general septic peritonitis; 2 are cases of general peritonitis without perforation; 1 a case of general septic peritonitis of unknown origin, though probably due to a perforation.

One of the perforative cases (Case 17) was a "walking typhoid," and had probably had general peritonitis for at least thirty-six hours before entering the Massachusetts General Hospital.

In all of these 14 cases *distinct warning symptoms* antedated equally distinct severe and diagnostic symptoms. The milder symptoms, which we must conclude marked the beginning of the peritoneal infection, were chiefly various degrees of abdominal pain and tenderness, either localized or general, complained of by the

[1] Glasgow Medical Journal, 1897, vol. xlvii. p. 103.

patient. All of these 14 cases were mild types except 4. In only 1 of the 14 cases was any complaint recorded of abdominal pain until the complaint ushering in the severe symptoms, and in the single exception to this the complaint of abdominal pain antedated the actual perforation by some weeks.

In 4 cases abdominal distention throughout the course of the fever is noted. In 9 cases there is no record of any abdominal complaint or abnormality until the peritoneal infection was under way. In every one of these cases recorded *complaint by the patient of abdominal pain* was followed by peritoneal infection. The severe symptoms followed these warning symptoms at various intervals in every case, and there can be little doubt that the severe symptoms, when they appeared, meant that the peritoneal infection had become general and alarming.

An analysis of these premonitory symptoms shows that in 6 cases the pain complained of was general abdominal pain; in 3 cases localized in the left iliac region; in 4 cases in the right iliac region; in 1 case in the lower abdomen; in 1 case general abdominal pain, and also pain in the rectum and bladder; in 1 case the pain began in the epigastrium and later became marked in the right iliac region. It is much to be regretted that the importance of this abdominal pain was apparently not appreciated, as shown by the case records.

In 3 cases *comparatively* complete physical examination is recorded as made at the time. In no case was there a record of as careful an examination of the patient in every detail as the importance of the symptoms demanded, so that our knowledge of the accompanying conditions of tenderness, muscular spasm, leucocytosis, pulse, and temperature is insufficient.

In 2 cases the complaint of pain was preceded by vomiting. In only 2 cases was a record of a leucocyte count made, and in these cases it appears that the blood-count was only done once. As will be shown under the head of "Leucocytosis as a Symptom," an isolated blood-count is of little or no value. In 1 case general abdominal tenderness and rigidity were noted, and in 2 cases there was general tenderness. In 4 cases there is no record of any physical examination, but a record *that morphine was given.* In 3 cases it is noted that the pulse and temperature were rising.

This warning abdominal pain preceded the severe symptoms by

hours and days; it appeared in 1 case sixty hours before; 1 case forty-eight hours before; 1 case twenty-four hours before (Case 17); 4 cases twelve to fifteen hours before; 4 cases eight hours before; 3 cases three to five hours before.

It is noteworthy that the 2 cases in which no actual perforation, but general peritonitis from other causes existed, had equally marked advance pain.

Cases 16 and 21, where the severe symptoms followed just as in the cases of perforation, point plainly to the reasoning that the early pain in these cases was due to local peritoneal infection, and that the severe symptoms were due to the establishment of a general infection.

The severe abdominal symptoms in every case determined the diagnosis and the decision to operate. In general these symptoms were those of general septic peritonitis, namely, general abdominal pain, severe; general tenderness and rigidity, with distention, collapse, poor pulse, and anxious facies.

In only 3 cases was there any vomiting.

The classical sudden fall of temperature is not present in many of the cases. The temperature fell somewhat in a few cases. In 2 cases it fell to normal, and began at once to rise; in 1 case it fell to and remained subnormal; in 3 cases a slight drop in temperature is noted; in 6 cases there was no fall of temperature, and in 3 cases it is recorded as rising.

In 8 cases a leucocyte count was taken at a time corresponding to these severe symptoms; in 4 cases it showed leucocytosis; in 4 cases it showed no leucocytosis. The leucocyte counts are, however, of only relative value, as will be considered later under the heading of "Leucocytosis as a Symptom."

In only 2 cases was a record of obliterated liver dulness made.

The constant symptoms in every case are abdominal pain, general tenderness and rigidity, with distention, associated with collapse and rapid, feeble pulse.

A comparison of the severe abdominal symptoms in the two classes of cases—the 7 cases where warning symptoms were not present, and the 14 cases with warning symptoms—show *distinct differences* in the severe symptoms in those in which the sudden intestinal perforation and extravasation came on without warning.

As has been stated, the severe pain, more or less localized, with shock and muscular spasm and tenderness, characterized the first set of cases, and the shock varied in the different cases. In 1 case the pulse was not over 100. There was no vomiting, no general abdominal tenderness or rigidity, and no distention in any case.

Contrasted with this first set of cases, the severe symptoms in the second set present a much graver picture. It is noteworthy that in the two cases in the first set, in which general peritonitis was the cause of the symptoms and not intestinal perforation, the picture corresponds to the severe picture in the second class of cases.

It should be noted that if the signs of actual perforation with extravasation are local to a great extent, as in the 5 cases of our first set, a careful examination of all cases at the warning complaint of pain might in many of them give us definite diagnostic signs, as in Case 3, for example.

A comparison of these two sets of cases—the 7 with sudden symptoms without perforation and the 14 cases with severe symptoms following premonitory pain—bears out the point that in most of them no positive diagnosis of perforation was made, but only a diagnosis of the general peritonitis resulting from the perforation.

The Time of Operation after Symptoms Appeared.

In the 7 cases with no warning symptoms operation was done within twelve hours in every case; 1 case within an hour and a half; 3 cases within four hours; 1 case within seven hours; 1 case within eight hours; 1 case within twelve hours.

At the operation general septic peritonitis was not evident to the eye in Cases 1, 3, and 7. In Case 5 it is noted as just beginning and not far advanced. In Case 4 the perforation was protected by weak adhesions, and no general infection had taken place up to the date of operation. In Cases 2 and 6 general peritonitis was further advanced and was evidently the cause of the sudden symptoms, so that only five operations can be said to have been for perforation itself and not for general peritonitis; and of these 5 cases, 2 cases, namely, Cases 1 and 4, may be said to have recovered from the operation, although Case 1 died at the end of five days from excessive intestinal hemorrhage. Of the 14 cases which had warning symptoms 9 were operated upon within five hours from the severe

symptoms, or from the time of positive diagnosis of perforation; 1 case within eight hours; 1 case within nine hours; 3 cases within twenty-four hours; 3 cases, however, were not operated upon for twenty-four hours after general peritonitis was plainly evident.

Reference to the annexed table will show that the average time of the operation after the early warning symptoms was twenty-three hours.

NUMBER OF HOURS ELAPSING BEFORE OPERATION IN THE 14 CASES WITH PREMONITORY SYMPTOMS.

After first pain and warning symptoms	20 hours.
" " " "	12 "
" " " "	48 "
" " " "	11 "
" " " "	15 "
" " " "	24 "
" " " "	20 "
" " " "	12 "
" " " "	60 "
" " " "	8 "
" " " "	48 "
" " " "	6 "
" " " "	12 "
Case of Bloom, No. 17	?
After severe symptoms	3½ hours.
" " "	8 "
" " "	24 "
" " "	3 "
" " "	3 "
" " "	9 "
" " "	5 "
" " "	3½ "
" " "	24 "
" " "	3 "
" " "	4 "
" " "	2 "
" " "	3½ "
Case of Bloom, No. 17	?

If it is granted that the early pain, etc., meant perforation or beginning peritoneal infection, and the severe symptoms meant general septic peritonitis, then it must be granted that operation took place from six to sixty hours after it was first indicated.

In all of these 14 cases the operation should be considered as primarily directed against the septic peritonitis and not the intestinal perforation. The recoveries from the operations in this class of cases are Cases 16 and 17. Case 9 is reported to have recovered from the operation for one perforation and to have lived eight days until a second perforation necessitated a second operation, followed by death. It has been seen in the analytical report of this case that such a view of it cannot be permitted. It seems just to decide that this case did well after the first operation, until the extensive necrotic changes in the cæcum involved the first sutured area and caused giving way of the sutures and a second extravasation.

Situation of the Perforation and Situation of the Damaged Areas.

We have in this series of cases 17 cases of true intestinal perforation and 2 cases of threatened perforation with damaged and necrosed peritoneum. In every case the perforation or impending perforation was in the ileum.

In 7 cases it was within one foot of the cæcum; in 4 cases it is noted as close to the cæcum; in 1 case two feet from the cæcum; in 1 case three feet from the cæcum; in 1 case four feet from the cæcum; in 5 cases the site is not recorded; in 3 cases it is recorded to have been the size of a "pin's head;" in 2 cases the "size of a dime;" in 1 case the size of a "split pea;" in 1 case to have been a large, irregular hole; in 1 case two perforations close together, near the cæcum. In only 1 case (Case 15) was a second perforation found at the post-mortem.

In Case 14 the perforated coil of intestine was found situated low down in the pelvis, and in this case the initial pain complained of was referred to the region of the rectum and the bladder.

The method of closure of the perforation in every case but one consisted of inversion of the hole with silk sutures. In 1 case (Case 11) the ulcer was resected by a V-shaped incision. In Case 10 two rows of silk Lembert sutures were used, causing extreme inversion of the intestinal wall. This case died within thirty-six hours with extreme abdominal distention and obstinate vomiting. At the autopsy it was found that the use of the two rows of sutures had reduced the lumen of the intestine to such an extent that it

only took the tip of the little finger, and that it was obstructed by a moderate amount of hard fecal matter. It seems legitimate to raise a query as to whether this case died from peritoneal infection or from intestinal obstruction, from the great inversion of the wall of the gut.

In 3 cases, in addition to suturing perforations or threatened perforations, additional suspicious thin places in the intestinal wall were inverted. This procedure, provided the condition of the patient justifies the expenditure of the extra time, is certainly advisable in all operations for typhoid perforation. It has been advocated by Sifton[1] and also by Hill in a case reported by Keen.[2]

In 7 cases out of the 21 the abdominal incision was median; in 2 cases the incision is not recorded; in 12 cases the primary incision was in the right iliac region. In only 2 cases are counter openings for irrigation and drains noted. The right iliac incision proved most capable of allowing speedy access to the infecting lesion. In 2 of the cases where the median incision was used it is especially recorded that long overhauling of the intestines was needed before the perforation was found. In 1 of the cases in which the median incision was used the time of operation is recorded as one and a half hours. Certainly the site of the infected areas in this series of cases points to the routine employment of a right lateral incision.

Peritonitis: Kind, Amount, with the Bacteriological Findings.

Unfortunately, the value of this series of cases is much impaired by the lack of bacteriological data concerning the nature of the general infection. If this series of cases furnished complete records of a careful physical examination at the appearance of the first symptoms in every case, and also complete bacteriological evidence concerning the virulence of the peritonitis resulting from the initial infection, we should be much better equipped to arrive at some definite statistical basis for establishing an approximate prognosis in such cases.

Three cases, namely, Cases 1, 3, and 7, operated on one and a half, three, and eight hours after the sudden onset of the perfora-

[1] Chicago Clinical Review, vol. iv., p. 368. [2] Loc. cit.

tion, had no visible macroscopical signs of general peritonitis. Case 1 lived nearly a week, and died from intestinal hemorrhage, and the autopsy showed no general peritonitis. Cases 3 and 7 both died within sixty hours, one with the symptoms of general peritonitis and the other without such symptoms.

There were, however, no bacteriological studies of the peritoneal infection in these three cases at the time of operation. Two of the cases may very probably have died from a virulent infection, which did not cause any visible signs.

Vincent[1] experimentally has called attention to the fact that a streptococcus peritoneal infection in typhoid is usually a fatal complication. Vincent's studies have been corroborated by Flexner and Fraenkel.[2] Cushing[3] reports a case in which operation was done within an hour or two after perforation, and at the operation no visible signs of general peritonitis were present. Cultures and cover-slip preparations from the fecal fluid pouring out of the perforation in the intestinal wall showed large quantities of streptococci, and the case died of streptococcus peritonitis.

It is perfectly within reasonable bounds to believe that one or more of the supposedly favorable cases in our series may have had a streptococcus infection. Certainly we have no evidence to the contrary.

Cases 2 and 5 show a beginning general peritonitis, as evidenced by gas and serous fluid free in the abdominal cavity, but indicated no injection of the peritoneal coat of the intestines. Both of these cases, so far as the macroscopical appearance went, seemed favorable, yet both died. Cultures taken in Case 5 showed a pure infection of the bacillus typhosus.

Case 4 had no general peritonitis, as has been stated. Case 16 was one of general peritonitis arising from the same cause as in Case 2, namely, damaged peritoneum; yet in Case 16 peritonitis was much more extensive macroscopically than in Case 2, being evidenced by sero-turbid fluid with fibrin flakes and with green fibrin patches on the intestines. Case 16 recovered; Case 2 died. Although Case 2 was a more severe typhoid, presumably the gen-

[1] Annales de l'Institut Pasteur, vol. vii. p. 141.
[2] Johns Hopkins Hospital Reports, 1895, vol. i.
[3] Philadelphia Medical Journal, March 3, 1900.

eral peritonitis in one case was caused by a virulent infection, and in the other by a non-virulent; yet no bacteriological proof is available in either case.

General septic peritonitis in typhoid arising from threatened intestinal perforation from the necrosed and damaged areas of peritoneum over the base of ulcers must be accepted as a not very uncommon occurrence. J. F. R. Gairdner[1] has reported 5 such cases.

To sum up in regard to our first class of cases, namely, 7 with sudden onset of symptoms, 3 had no general peritonitis evident to the eye; 1 case had limiting adhesions around the perforation, with no general peritonitis; 2 cases had slight evidence of general peritonitis. These are all of them the most favorable cases for operation, for it must be said of them that operation was actually directed against the infecting cause and not against the resulting general infection.

The bacteriology was studied in only one of these cases, and in this one a pure culture of the typhoid bacillus was found.

It is a fact that the typhoid bacillus has been very rarely found in the peritonitis of typhoid fever, possibly because, through delayed operation, cultures have not been taken until the typhoid bacillus was overgrown.

It is possible, and probable, that the others of these early and seemingly favorable cases for operation may have had a general virulent infection either with typhoid bacilli or streptococci. It is past controversy that fatal peritoneal infection can have taken place without causing visible macroscopical signs at operation or autopsy. Of the 14 cases of gradual onset or with early warning symptoms, in every one visible peritonitis was found at operation, and in the majority of cases it was evidently of comparatively long standing.

Comparing the two sets of cases, namely, the 7 cases with sudden onset and the 14 with gradual onset, we find that in operations done on the cases of sudden perforation within one to eight hours after the first symptoms there was found no general peritonitis, but at most a very slight beginning peritonitis; but operation done on those of gradual onset, within one to eight hours after the severe

[1] Glasgow Medical Journal, vol. xlvii. p. 97.

or diagnostic symptoms, found extensive general peritonitis—so extensive that in several cases the operator noted that this peritonitis must have existed many hours longer than the symptoms would lead one to suppose. The conclusion is plain that in these cases the perforation or the beginning peritoneal infection took place at a time more or less remote from the severe and diagnostic symptoms.

These 14 cases are cases of operation for general peritonitis which had existed for a longer or shorter time—in 1 case originating in a ruptured mesenteric gland; in another, threatened perforation; in one from an unknown cause; in 11 from intestinal perforation.

The prevailing type of peritonitis noted was the seropurulent, with fibrin flakes in the turbid fluid and adherent fibrin patches on the intestine. Nine cases are noted that had feces or fluid fecal matter in the intestinal cavity or fluid with a fecal odor. All of these cases were intestinal perforations. Two cases of intestinal perforation note a cloudy turbid fluid without fecal odor.

Case 21 was a case of general seropurulent peritonitis originating in a ruptured mesenteric gland. Cultures showed this to be a pure infection of bacillus typhosus. In Case 17 punctate hemorrhages on the intestinal wall are noted, and brownish fluid in the peritoneal cavity without odor.

It is greatly to be regretted that in only 4 of these 14 cases were any bacterial cultures taken, and in certain of these the question arises as to their value, because of our incomplete knowledge as to how they were taken and because of incomplete reports of the differentiation of the various bacteria found. Flexner[1] and Cushing[2] dwell upon the necessity of making cover-slip preparations as well as plate cultures at the operation from the abdominal contents in cases of peritonitis, because of the well-known fact that the bacillus coli communis overgrows the other organisms in the mixed infection. Cushing says: "Undoubtedly the colon bacilli, being more in evidence, were frequently held responsible for peritoneal infection due to more virulent but culturally less active organisms."

Case 14 is recorded as showing an infection with colon bacilli and "other varieties of bacteria." Case 20 is recorded as having turbid peritoneal fluid with fibrin flakes, infection with colon bacilli.

[1] Loc. cit. [2] Loc. cit.

Case 21, resulting from a ruptured mesenteric gland, gave a pure culture of bacillus typhosus. Case 15 is reported to have been a specially foul-appearing general peritonitis, in which the infection was colon bacilli, and "many others not differentiated." The 2 cases (Cases 5 and 21) in which the peritonitis was found to be due to a pure infection of bacillus typhosus died—one within twelve hours and one on the fourth day.

The finding of the bacillus typhosus as the infecting organism in cases of peritonitis is exceedingly rare. At most, but five cases, including the two cases reported in this series, have been published. It may be suspected, reasoning from the evidence furnished by Case 5 and Case 21, that when it does occur it is probably virulent and fatal.

Diagnosis.

The diagnosis of the peritoneal infection within a sufficiently reasonable time from its beginning is a question of the greatest importance to physicians and surgeons. So far, our study of these cases has shown us that the diagnosis in 14 cases out of 24 was apparently made later than it might have been, and in 7 cases only once was it made as soon as possible, and that in 3 cases a mistaken diagnosis was made.

It seems fair to suppose that the majority of cases of intestinal perforation present a slow intestinal infection or a gradual onset, or that actual perforation may take place without fulminating symptoms. Cushing has referred to what he calls a "pre-perforative stage" or a "pre-extravasation stage," and has attributed the early complaints of pain to a slight involvement of the serosa and possibly to omental adhesions. He understands by his "pre-perforative stage" the "whole period between the first involvement of the serosa, with the formation of customary adhesions at this point, until these adhesions (which may for a time constitute the floor of the ulcer after the serosa has given way) have themselves become broken down, and general peritonitis has taken place." This condition of things is well illustrated in our Case No. 4, which is a typical case of pre-extravasation, because of delicate protecting adhesions.

It would seem, however, from a study of our cases, that the

formation of protecting adhesions in perforation or threatened perforation of the ileum is exceedingly rare. Monad and Van Verts[1] state that in their study of this condition, adhesions, however slight, almost never occur when the perforation is situated in the ileum; and they further state that peritoneal infection is not always a rapid fulminating affair; that it may occur slowly from what they call "propagation"—that is, migration of the bacteria through the necrosed and damaged intestinal coats, and that this form of infection is no less worthy of consideration than the rapid infection from sudden intestinal rupture and extravasation of intestinal contents.

Intestinal ulcers certainly may have a pre-perforative stage, and by this we mean a stage of local peritoneal infection and bacterial involvement of the peritoneal coat—whether or not adhesions exist. This local infection may cause general infection without adhesion formation and without perforation. The pre-extravasation stage properly means a period of time after local peritonitis has taken place in which there is no extravasation of intestinal contents, either because of the necrosed portion of the intestinal wall remaining in place without dropping out, as in Case 16 or in Case 2 of our series, or because of adhesions, as in Case 4 of our series. Local infection of the peritoneum causes pain of greater or less severity. This pain may not be appreciated and complained of in very sick and stupid typhoids, but in mild cases may be just as prominent a feature as the pain from the local peritoneal infection of appendicitis before perforation has taken place.

Our series of cases shows that this early pain was absent in only 7 cases out of 21; 5 of these 7 cases were mild cases, in which sudden rupture of the serosa and extravasation took place; 2 cases with equally sudden symptoms had a septic peritonitis already under way, which cases were so sick and stupid that it was impossible to diagnose the beginning of the general infection.

Fourteen cases, as has been seen, had early warning pain, earlier by a definite number of hours than the severe symptoms, and all these cases were found to be far advanced in general peritonitis at the time of operation. These early symptoms undoubtedly meant beginning peritoneal infection, as is shown by the after develop-

[1] Revue de Chirurgie, 1897, p. 169.

ment, and the severe symptoms meant general septic peritonitis then existing. Whether these early symptoms meant a necrosed serosa without perforation, or a pin-point perforation protected or not protected by delicate adhesions, it is positive that general septic peritoneal infection started at a time coincident with these early symptoms and not coincident with these severe ones.

It must be admitted that these 14 cases had advanced general peritonitis at the time of operation; that they had signs and symptoms antedating the symptoms of peritonitis; that the severe symptoms in the cases of actual perforation differed in no way from the severe symptoms in the cases of general peritonitis from other causes of infection; and if this statement is true, then the diagnosis of these cases should have been made before these severe symptoms set in, and, therefore, a decision as to what symptoms are of importance in making a sufficiently early diagnosis of peritoneal infection in these cases is of the utmost necessity.

From a study of these cases and also of the cases reported by Cushing it would seem that complaints of abdominal pain in any typhoid case, especially if localized, and especially in cases of mild type, should be regarded as serious danger signals. We have already seen that in our sick and septic cases the condition of the patient may be such that moderate pain may not be noted, and that therefore a complaint of abdominal pain on the part of such a sick case may mean an established general peritonitis. (See Cases 2 and 6.)

In the mild cases of typhoid complaint of abdominal pain should lead to a strong suspicion of beginning peritoneal infection through a pre-perforative stage, or of a slow peritoneal infection through perforation, with or without temporary adhesions; or of a beginning infection from some other source than the intestine, as in Case 21. This plan may vary in severity and locality. It is most frequent in the right iliac region, and is most often associated with localized tenderness and spasm. To confirm the suspicion of beginning peritoneal infection a leucocytosis, steadily rising, during a few hourly counts, at least, should accompany this pain. Vomiting is rare. The temperature generally rises and the pulse also.

It cannot be too strongly emphasized that abdominal pain, especially if localized, complained of by the patient in the mild or

moderately severe typhoids, is not a frequent occurrence unless it means peritoneal infection, localized or general. By pain we do not mean the discomfort or uneasiness accompanying meteorism or distention by gas.

We have made a study, bearing upon this point, of 70 cases of typhoid fever at the Massachusetts General Hospital occurring in the last two years, and have found, according to the records, that in the majority of cases of the mild and moderately severe typhoid no genuine abdominal pain whatever was complained of, even in the presence of distention, diarrhœa, and hemorrhage. Seventy cases: 20 severe typhoids and 50 mild; 7 cases died. In only 8 cases was any abdominal pain recorded as a complaint (11.4 per cent.), and 4 of these cases died (1 case with probable certain perforation or peritonitis, 1 of pneumonia, and 2 cases with suspicious symptoms of peritonitis). The other 4 cases had slight and transient abdominal pain, and recovered. Abdominal distention of more or less extent was noted in 10 cases, without any pain. Intestinal hemorrhages are noted in 8 cases, but pain accompanied these in only 1 case. Diarrhœa is recorded as marked in 3 cases, but in only 1 was any pain, and in this slight.

With reference to this same point the records of the Boston City Hospital have been gone over for a year. Pain is recorded as complained of in 22 cases out of a total of 160 cases; of these 22 cases 5 are included among those operated on, which leaves 17 cases with pain, or about 10.6 per cent. of the total.

Localized muscular spasm and localized tenderness are diagnostic signs of the utmost importance associated with pain and leucocytosis.

The question as to whether the site of the perforation or the region of the beginning peritoneal infection materially affects the prognosis both of unoperated and operated cases is one that needs discussion. The fact that the appendix may be the seat of the typhoid perforation was first noted by Dr. R. H. Fitz, and the relation of this fact to the prognosis in cases of typhoid perforation was thus stated by him: "The probability of its occurrence (perforative appendicitis) furnishes the best solution to the prognosis of intestinal perforation in the latter disease (typhoid fever). Most cases of recovery from symptoms of perforation of the bowel in typhoid fever are those in which an attack of appendicitis is most closely simulated, while the

fatal cases of perforation of the bowel in typhoid fever are, in the great majority of instances, those in which other parts of the bowel than the appendix are the seat of the perforation."

This set of cases does not furnish any case in which the perforation was appendicular. Fitz found this variety of perforation in 2 per cent. of 167 cases. In a series of cases operated upon—*i. e.*, our own set, 24; Cushing's, 8; and Finney's, 3; 35 in all—no instance occurs. Gairdner's[1] 47 cases included only one of *perforated appendix.* Perforation in the appendix can only have a more favorable prognosis because of its occurrence in a fixed portion of the bowel in a remote region where the chances of the peritoneal infection being shut up by protecting and life-saving adhesions are greater.

It is certainly misleading to state that most cases of recovery from symptoms of perforation are those in which an attack of appendicitis is closely simulated because—as can be plainly seen from a study of our list of cases—many of them had beginning symptoms which suggested appendicitis, and yet the perforation was in the ileum, and the peritoneal infection became general and fatal. It is imperative that we should not be prevailed upon to wait operation in the hope that the perforation may be in the appendix, considering that the chance of localizing the infection by delay offers more hope to the patient than speedy operation, because the attack began with right iliac pain and tenderness and muscular spasm. The better teaching is that perforation of the appendix may occur in typhoid, although *rarely;* that when it does occur the infection may be localized, as in any case of perforating appendicitis; but the great majority of cases of perforation of the bowel in typhoid fever may simulate an acute appendicitis.

A study of our whole list of 27 cases shows the following: Eleven cases had initial symptoms referred to the right iliac region, with one or more of the symptoms of localized pain, tenderness and spasm. Any one of these cases might have been suspected as the appendicular variety, and delay counselled because of the apparent localization of the signs; but 9 cases were perforations of the ileum, followed in all but one by general infection, and 2 had no cause for symptoms.

[1] Loc. cit.

In only 3 cases pain and tenderness, etc., were initial in the left iliac region. One was a case of general peritonitis from a suppurating gland, and the other two cases were very sick cases, in which the peritonitis had become extensive and general before any symptoms were noted. In 7 cases the pain and tenderness with rigidity were general. In 1 case locality of pain is not given.

Therefore, we may conclude that the majority of cases of perforation have initial symptoms referred to the right iliac region; that in a very small percentage of all such cases is the perforation in the appendix; that general abdominal pain and symptoms, or symptoms and signs referred to the left side point to the existence of a general peritonitis, the onset of which has been gradual and not definitely noted.

Leucocytosis as a Diagnostic Symptom.

A careful comparative white blood-count at frequent intervals in the presence of abdominal pain in typhoid may furnish the most valuable evidence of beginning peritoneal infection. A full and complete knowledge of leucocytosis in typhoid peritonitis has not been reached. Thayer, in 1892, first showed that in typhoid fever the white blood-corpuscles are less than normal, or, in other words, that a condition of hypoleucocytosis exists, and that the smallest number of leucocytes is usually found at a period of time corresponding to the height of the fever. Cabot, in 1897, reiterated these facts and pointed out that a low leucocyte count in typhoid meant freedom from septic complications. Our study of 70 typhoid cases at the Massachusetts General Hospital is merely corroborative of the statements of Cabot and Thayer. The majority of cases at entrance had a hypoleucocytosis of about 4000; the lowest count in an uncomplicated case was 1800. Septic complications, as phlebitis and otitis media, caused a leucocytosis. In nearly all the cases, however, only one white count—the one at entrance—is recorded; and even when this early count was high—over 9000—no other record is available. Certainly more frequent counts should be made in the future. The fact that leucocytosis in typhoid means inflammatory complications in the majority of instances, and that leucocytosis was present in peritoneal infection, was noted by Cabot (1897); and Finney, in his paper on "Typhoid

Perforation" (1897), considered the most important symptoms of perforating typhoid ulcer to be "marked increase in the number of white blood-corpuscles in association with continued abdominal pain." It does not appear that a full realization of the importance of a falling leucocyte count or the absence of leucocytosis in general peritoneal infection is held by a majority of medical men.

Cabot stated that certain cases of general peritonitis would show no leucocytosis because of their being too sick to react against the infection.

Cushing, in his two papers on this subject, seems to have most carefully studied leucocytosis as a symptom, and his work strongly suggests that a white blood-count, steadily rising from the first complaint of abdominal pain (which is confessedly the first warning of local or general infection), with certain fluctuations, reaches a maximum point, and then as steadily falls. This he aptly calls the wave of leucocytosis, and raises the question as to whether a falling count or an absence of leucocytosis (other symptoms being present) may not be diagnostic of a well-established general septic peritonitis. He considered it rational to suppose that the enormous migration of leucocytes to enter into the seropurulent exudation was a sufficient reason for the falling or deficient white blood-count in general peritonitis. This point is a very important one to settle, for diagnostic reasons. Cushing's conclusions, from a careful study of leucocytosis in his cases, are here given: "If this septic complication, namely, complication causing leucocytosis, is a peritonitis which remains localized, associated possibly with a pre-perforative stage of ulceration or with a circumscribed, slowly forming peritonitis after a perforation, it may be and usually is signalized by an increase of leucocytes in the peripheral circulation. If, however, a general septic peritonitis follows, the leucocytosis may be transitory and overlooked, as it disappears concomitantly with the great outpouring of leucocytes into the general peritoneal cavity.

"In order that the white blood-count be of any diagnostic value whatever in the presence of abdominal symptoms it is essential that, for the purpose of comparison, previous counts have been made. An individual count at such a critical time may be misleading—in the first place, because a condition of hypoleucocytosis often is a characteristic of the fever, and a count comparatively within normal

limits, of from 8000 to 10,000, may actually represent a double increase in the number. Secondly, because by a single count the transient wave of leucocytosis may entirely escape notice.

"The flood-tide of this increase is a transient affair, lasting but a few hours in some cases, and may in consequence entirely escape observation, since there ordinarily is a following rapid diminution in number, corresponding to the spread of peritoneal infection. In some instances, when the process for the time remains localized, and in cases in which the pre-perforative stage exists, the leucocytosis may be of longer duration, the condition being analogous to that associated with acute appendicitis (typhoidal or otherwise) before perforative peritonitis has occurred. Suppurative complications of typhoid, here or in other situations where they remain localized processes, have ordinarily a persisting leucocytosis, as is well known."

These conclusions of Cushing are re-enforced by careful observations, and seem to give the best interpretation of leucocytosis in this class of cases. Whether absence of leucocytosis in the face of symptoms of peritonitis means well-advanced general peritonitis in every case has not been proven absolutely. Certainly one sure thing is that a single isolated blood-count on the appearance of abdominal symptoms may be of little or no value. In one of Cushing's cases of perforation an hourly blood-count showed that the white corpuscles rose in two hours from 4800 to 10,400, and in an hour and a half later dropped to 7000. In another of Cushing's cases of intestinal perforation a drop of 20,000 in three hours after the probable time of perforation is noted. The appearance of leucocytosis in the presence of abdominal pain may, however, be misleading as a diagnostic symptom of peritoneal infection.

As is well known, the existence of a septic focus, an abscess, or a septic phlebitis elsewhere might furnish cause for the leucocytosis coincident with abdominal symptoms. One or more cases have been reported in which the symptoms of peritoneal infection, including leucocytosis, led to an exploratory laparotomy, with negative findings. Cushing has had such a case. Case 23 in our series is also such a one. Finney has been led to an exploratory laparotomy in which the symptoms suggesting intestinal perforation including a leucocytosis were probably due to an iliac thrombophle-

bitis. This case recovered. It has been found by Cushing that a post-operative leucocytosis occurs after all abdominal operations.

With these facts and theories in mind as representing the latest opinions in regard to leucocytosis as a symptom, reference to our series of cases with a view to find corroboration of these facts furnishes very little of value because of the lack of comparative counts. In almost all of the cases only one blood-count was made.

To take our cases in detail, the leucocyte count is only recorded in 11 cases of the 21 in which perforation or peritonitis was found. In the first set of cases, namely, those without warning symptoms, the leucocyte count is recorded in 4 cases. In Case 4 (the case of perforation protected by local adhesions) a leucocytosis of 14,300 was found at an unknown number of hours after the onset of abdominal symptoms. No other count is recorded. In Case 5 one count at the onset of symptoms showed 6000; no other count. Case 6 showed a leucocytosis of 13,200. This case was one in which perforation and localized abscess formation took place without any diagnostic symptoms at a time probably remotely preceding the severe symptoms which demanded operation. Occasional comparative leucocyte counts as a matter of medical routine might have led to the suspicion of a septic complication. Case 7 showed a white count of 8600 at the onset of the symptoms; no other count is recorded. The other 3 cases of our first set have no record of any leucocyte count.

Taking our second set of cases, namely, the 14 in which premonitory symptoms existed, as we have seen, it would have been of the *greatest importance diagnostically* to have known what the white blood-count had been for several days before the symptoms, and also to have known what the white blood-count at early intervals after the occurrence of abdominal pain was; yet in only two cases was there any leucocyte count taken at this time, and then only one isolated count in each case is recorded.

Case 16 had a white blood-count of 6900 two days before he complained of abdominal pain. At the first complaint of pain a count of 8000. Then no further leucocyte count was taken for twenty-four hours; but when severe symptoms (which meant general peritonitis) set in a white count equalled 17,200. Certainly in this case frequent and comparative blood-counts might have con-

tributed much to our knowledge of a rising and falling count. Case 15, seen after the warning complaint of pain, had a white blood-count of 31,000. Twenty-four hours after, when general peritonitis had set in, the white count had dropped to 23,000 and 17,000. Only these three counts are recorded.

It is much to be regretted that in this series of cases in which 14 had premonitory symptoms, such slight knowledge in regard to the diagnostic value of the white blood-count is available. In Case 14 the blood-count at the time of the first abdominal symptoms showed 10,000 whites, but no other count was taken. Six cases of the 14 record no blood-count at the occurrence of either mild or severe symptoms. In 6 cases the only blood-count was made when severe symptoms appeared. In Case 12, a case of extensive peritonitis at operation, the white cells were 3800. In Case 13, also a case of extensive peritonitis, the white cells were 5400. In Case 8, also a case of general peritonitis, the white cells were 7300. In Case 2 they were 8000 just before operation.

Here are four cases in which an isolated blood-count, taken when peritonitis had become general, showed no leucocytosis. Whether a previous leucocytosis had existed, and whether the absence of leucocytosis in the presence of general peritonitis is a diagnostic sign, cannot be determined because of the absence of comparative counts in all of these cases.

Case 9 had a leucocytosis of 16,000 after general peritonitis was evident. Ten days before the count was 14,000. No interval counts are recorded.

Case 10 had a white count of 14,000, with the symptoms of general peritonitis. At entrance to the hospital, ten days before, his white count was 6500. No other counts are noted.

It is not possible to establish anything new and valuable in regard to leucocytosis as a symptom from the study of these cases, because of the lack of sufficient data. The one conclusion is that the leucocyte counts in typhoid cases should be sufficiently frequent to be of comparative value; that any complaint of abdominal pain or the appearance of abdominal symptoms demand frequent counts.

The question of diagnosis and the relative value of abdominal symptoms and leucocytosis as deciding for operation is illustrated in a negative way in Cases 22, 23, and 24. Cases 22 and 23 were

mild or moderately severe typhoids, practically convalescent in the fourth and sixth weeks of the disease. Case 22 had no leucocyte count, and it seems questionable whether it would be justifiable to operate upon a case with such abdominal symptoms without the corroborative evidence of a leucocyte count. It has been done, however, in other cases (the case reported by Herrington and Bowlby[1]). Case 23 had practically the same abdominal signs and symptoms as Case 22, except that there is no record of the temperature at this time, which in Case 22 was rising from a normal curve, and Case 23 had also a leucocytosis of 12,000 one hour before the operation. While this leucocytosis is not large, the white count had risen from 9000 twelve hours before the operation. Neither of these two cases seems to have been very sick or to have had any great amount of shock. Case 24 seems to have been a case of typhoid septicæmia, in which no certain cause for the abdominal symptoms was found. No leucocyte count and no bacteriological cultures are recorded in this case. Probably it died from typhoid fever, although the presence of a green, necrotic fibrin patch found on a loop of the intestines at the operation leaves room for the thought that the abdominal symptoms and death may have been caused by a virulent peritoneal infection.

Results.

Of the 21 cases in which the local or general peritoneal infection was found at operation 3 cases recovered absolutely—that is, 14.3 per cent. recovered. In Case 4—a case of operation in the pre-extravasation stage—it is noted by Dr. F. S. Watson that the protecting adhesions were very slight and delicate, and that in Dr. Watson's opinion they would not have long resisted fecal extravasation.

The two other cases which completely recovered are Cases 16 and 17, both cases of general septic peritonitis. Together with Abbe's[2] case they prove that it is not impossible to save cases of general peritonitis in typhoid fever. The bacterial infection, however, in both of these cases, as well as in the case of Abbe's, was not determined.

[1] Medico-Chirurgical Transactions, London, vol. lxxx. p. 127.
[2] Medical Record, 1895, vol. xlvii. p. 1.

Case 1 properly should be classed as a recovery from an operation for intestinal perforation in typhoid, for death occurred from intestinal hemorrhage five days after the operation, and the autopsy showed the suture tight and no general peritonitis. If this case can be classed as a recovery we have four recoveries from operation from acute peritoneal infection in typhoid, or 19 per cent.

Case 9 cannot be considered as recovering, but it is a case of death caused by giving way of the intestinal sutures put in at the first operation.

Taking our 24 cases of typhoid fever which were operated on, 21 with abdominal infection and 3 with no infection found at operation, we have 6 cases of recovery from laparotomy in typhoid fever, or 25 per cent.

Cases 22 and 23 are noteworthy as showing that the mere abdominal operation in a slight or moderately severe typhoid is not a very fatal thing when no peritoneal infection is present. Case 23 was also not a very favorable subject for any operation, because of cardiac and renal complications, yet both these cases made uneventful recoveries from the operation. In Case 22 an appendectomy was done for an old, chronic process in the appendix. In Case 23 the operation was simply exploratory. Two of Cushing's reported cases further show that an exploratory laparotomy or a simple appendectomy in a mild or moderate typhoid is usually well borne. We have seen that the 5 cases (Cases 1, 3, 4, 5, and 7) were especially favorable cases for operation. Three of these died, and they were all cases that could have stood laparotomy just as well as Case 22 or Case 23 had it not been for the peritoneal infection, the nature of which was undetermined in two cases and found to be the bacillus typhosus in one. These 3 fatal favorable cases point to the fact that a fatal peritonitis may set in within from one to two hours after perforation. Of these 3 cases Case 3 died on the third day, Case 5 on the fourth day, and Case 7 on the second day.

Of the 14 cases in our second set, in all of which operation found more or less extensive peritonitis, and in regard to which it may be said that the operation was directed against the peritonitis primarily, twelve died; 1 lived eight days and died from secondary extravasation. All the others died within fifty hours after the operation: 2 in six hours, 7 in thirty-six hours, and 1 on the operating-table.

If we grant, for the sake of argument, that the sick typhoids, 6 in number, might have died from their typhoidal condition complicated by an abdominal operation, even if peritonitis had not been present, we still have 8 mild cases in which the cause of death was probably a peritoneal infection, and not the operation itself.

Calculating statistics of the operative treatment of general peritonitis from any cause is foolish business. The chances for success in such treatment depend on so many factors: the amount and virulence of the infection, the condition and resisting powers of the patient, the differing operative technique of different men, the time of operation, the kind and amount of anæsthetic used, etc. In trying to find out why some of these cases lived and some died it would be well to take only the 15 mild cases, throwing out for the time being the 6 severely sick typhoids as doubtful cases for standing the shock of the abdominal operation, leaving ourselves 15 mild typhoids for consideration. Of these 5 had perforation without any warning symptoms, and were operated upon very speedily thereafter; 2 recovered, one because the operation was done in the pre-extravasation stage—a rare event; 3 died from peritoneal infection from the intestinal extravasation, although no macroscopical signs—or, at most, slight signs—of general peritonitis were present at the operation. Ten of these mild cases had general septic peritonitis at the time of operation; 2 recovered.

When we consider the reasons for the recovery of 2 of these cases and the death of 8 we are brought face to face again with insufficient recorded data. The time of operation is recorded in only 3 of the fatal cases: 1 case, thirty minutes; 1 case, thirty-five minutes; 1 case, one and a half hour.

The time of operation in the cases that recovered is not noted. The kind of bacterial infection in the cases that recovered is unknown. In 1 case that died it was an infection of bacillus typhosus; in 1 case infection of the colon bacillus and other doubtful bacteria.

Ether was the anæsthetic in every case; but the amount given, the time the patient was kept under it, and the effect on the pulse are in no case recorded.

Cushing has enthusiastically endorsed the use of cocaine anæsthesia in exploratory laparotomies in acute abdominal infection in

typhoid. He has not, however, proved in his article that the majority of his cases were any better off than the cases operated upon under ether. It is not the feeling of this committee that operation under cocaine anæsthesia is advisable in cases of mild typhoid whose general condition of mind and body is fairly good, because rationally the shock to the mental and physical organism from an abdominal operation, with all its attendant manipulation, to a conscious patient, must be greater than the judicious administration of ether. In certain cases of advanced peritonitis in which the patient is sick or nearly moribund, stupid, and unintelligent the use of local anæsthesia may be advantageous.

Irrigation of the peritoneal cavity with hot salt solution or hot sterile water was practised in every case of general peritonitis but one, viz., Case 16. In this case careful wiping out of the cavity with gauze was done. Drainage with gauze or with tube and gauze was used in every case but two, both of which died. It does not appear from available data that these variations in technique affected the result. The surgical opinion is practically unanimous the world over, that the operation for septic peritonitis must include free incisions, careful cleaning of the abdominal cavity by wiping, irrigation, and free drainage.

It is impossible to work out by percentages the chances of recovery in cases of intestinal perforation and peritoneal infection in typhoid fever. It is a question of peritoneal infection (kind, amount, and virulence), together with the condition and resisting powers of the patient, who has already contended with another disease. It is not the mere fact of operating in these cases that kills them, and it cannot be said that the typhoidal condition forbids an operation.

It has been shown that a majority of the cases of perforation and infection are mild typhoids, and it has also been shown that abdominal operation in the absence of infection is not necessarily fatal, but, on the contrary, is well borne. The peritoneal infection is the thing that kills in the majority of cases.

A peritonitis from a perforation of the intestine in typhoid may be caused by virulent or non-virulent organisms just as in any other perforation of the bowel. Most of the typhoid perforations operated upon in this series of cases and all cases hitherto published

have had a general peritonitis that would kill a majority of the men who had contracted it from other causes than typhoid, namely, perforated appendix or wounds. General peritonitis of the intestinal variety in a strong man, without typhoid fever, is a very fatal affair, and the chances of a recovery from operation in any case cannot be established by statistics except in a general way.

Conclusions.

This series, unfortunately, leaves much to be desired in the way of accurate and carefully reported study of many of the cases in the light of the most recent experience; but from the foregoing analysis of the material we can definitely conclude that:

1. In many very sick typhoids, perforation or peritoneal infection cannot be diagnosed until the results are already wide-spread and of fatal extent. The chances of a fatal issue from an abdominal operation in such cases are overwhelming.

2. In mild typhoids of fair general condition an abdominal operation is readily borne, provided no peritoneal infection is present.

3. A small number of mild typhoids may have sudden perforation with free extravasation. In these the symptoms are fulminant, but localized to a great extent, and in these

4. Operation must be done at once, for general infection may become past relief in from one to five hours, and walling off of the perforation by protecting adhesions is so rare as not to be counted upon.

5. In the majority of mild cases, beginning infection (whether from perforation or not) is marked by comparatively slight symptoms—local pain, tenderness, spasm, and leucocytosis. The severe following symptoms mean general peritonitis.

6. These warning symptoms demand serious consideration and study, but in many cases are either not rightly understood or not acted upon.

7. Complaint of abdominal pain in a case of typhoid should always lead to a suspicion of beginning peritoneal infection.

8. Frequent leucocyte counts are needed in every case of typhoid. In the presence of abdominal pain an hourly count is necessary.

9. Pain associated with local tenderness and muscular spasm and a rising white blood-count points in most cases to an operation; in all cases to a surgical consultation.

10. In not a few of this series of cases operation was imperative a varying number of hours before it was done.

If it can be appreciated that the severe symptoms more often mean general peritonitis, it must be understood that the milder and earlier symptoms are the important ones.

CASES.

CASE 1. Seeley.—Male, aged thirty-two years; white. Drs. Bowditch and Thorndike, Boston City Hospital, September, 1899. Sudden perforation. Operation within three hours from first symptoms. No general peritonitis. Death five days after from intestinal hemorrhage. Uneventful until the sudden abdominal symptoms.

Mild course. Widal positive. Diazo (?). No complications. No abdominal complaints. Not a sick man. End of sixth week, forty-second day, operation. Ether. Time not known. Incision, right iliac. Irrigation. Gauze drainage.

Sudden intense abdominal pain, not localized. Marked shock. Pulse 150. Temperature 102.6°. No leucocyte count recorded. No fall of temperature. No vomiting. Operation three hours after. No general peritonitis. Intestinal contents in abdominal cavity; fluid fecal matter. Perforation in ileum, two feet from cæcum. Closed with silk. No cultures. Excellent result for five days. Operation for the perforation successful. Five days after, excessive intestinal hemorrhage causing death.

The autopsy showed that the operation was a success. No general peritonitis. The suture was intact and protected by adherent intestines with slight local peritonitis, from which the colon bacillus and staphylococcus albus were grown. Cultures from rest of abdominal cavity negative.

CASE 2. Bowler.—Male, aged twenty-five years, negro. Drs. G. B. Shattuck and F. B. Lund. Boston City Hospital, October, 1899.

A case of general septic peritonitis from necrosed patches of peritoneum, *without perforation. Symptoms of perforation, however.* Moribund at operation. Death.

Severe course. Widal positive. Diazo(?). Abdominal pain constant. Fourth week, twenty-second day. Operation. Ether. Time (?) Incision, right iliac. Irrigation and drainage. Very sick case. Temperature high. Delirious. Abdominal pain and tympanites at frequent intervals. Two intestinal hemorrhages before operation (two days before).

Sudden chill, shock, collapse, rising temperature and pulse. Distention. *No vomiting.* Operated on seven hours after, when in *moribund* condition. *No leucocyte count. No perforation. Two necrosed patches* in wall of ileum over ulcers. *General peritonitis.* No cultures made. Gas and serous fluid escaped. Intestines clean and not injected. Several necrotic areas. Necrosed places, inverted with silk. Death in eighteen hours. Cause, peritoneal infection and typhoidal state. Compare this case with Case 16. This

case had sudden severe symptoms from peritonitis without perforation. An unfavorable case from all points of view.

Peritoneal infection from necrosed patches, *probably* virulent, whereas in Scappacci's case infection from necrosed patches probably non-purulent, with the abdominal pain and distention marked. Specially associated with hemorrhages, careful white blood-count at frequent intervals might have been suggestive.

CASE 3. McCann.—Male, aged thirty years, white. Dr. F. C. Shattuck and Dr. Warren. Massachusetts General Hospital, January, 1899. Sudden perforation without warning. Operation within two hours. Death in three days. Mild course. Widal positive. Diazo positive. Bronchitis. No abdominal complaints. Fifth week, thirtieth day. Incision, right iliac. Irrigation. Drainage, gauze. Ether. Time of operation (?). Mild fever complicated by hemorrhagic bronchitis. Intestinal hemorrhage two days before perforation. No warning. Patient comfortable, when sudden sharp pain in right iliac region with great tenderness and muscular spasm. No white count at this time. White count two days before, 3800. White count at entrance, ten days earlier, 10,000. No vomiting. Temperature subnormal, but began soon to rise. Pulse below 100. Operation one and a half hours after. Perforation in ileum, site not mentioned. No general peritonitis. Some free fluid. No bacteriology. Death on third day in sixty hours with symptoms of general peritonitis. No autopsy.

CASE 4. Scott.—Male, aged twenty-eight years, white. Drs. Withington and Watson. August and September, 1895. Perforation. Localized peritonitis. Operation in pre-extravasation stage. Recovery. Mild course. No Widal test made. Diazo positive. Rose spots. Eleventh week in a relapse. Operation. Ether. Time of (?). Incision right iliac over induration. No irrigation. No drainage. Long course, one or two relapses. No special complications. Twenty-three days before perforation two or three hemorrhages. No abdominal pain recorded, but some tympanites. Without warning sudden severe pain in right iliac region at 2 A.M. Temperature did not fall, but rose. Pain steadily worse. Pulse rapid and weak. Some cyanosis and prostration. Muscle spasm on right side of abdomen. Dulness and indurated feeling to right of umbilicus, "size of hand." No distention. No vomiting. "The symptoms of local pain and rigidity increased while patient's general condition improved." Leucocytosis 14,350. Operation twelve hours after first pain. A loop of ileum adherent to parietal peritoneum around a perforation size of a dime—well defined area of local peritonitis. Limiting adhesions delicate. "Every probability that these adhesions would not have resisted fecal extravasation long and that a general peritonitis would have resulted if case was left to itself." (Watson). Perforation closed. Recovery uneventful. No cultures.

CASE 5. Dolan.—Female, aged twenty-five years, white. Drs. George B. Shattuck and Lund. Boston City Hospital, November, 1899. Perforation. Beginning general infection with typhoid bacillus. No definite warning

symptoms. Death. Mild course. Widal positive. No complications. No abdominal complaints. In second week, twelfth day. Operation. Ether. Time, thirty minutes. Incision, median. Irrigation. Drainage. Uneventful till twenty-six hours before operation, then hard chill (no other record at this time). Next A.M. (twelve hours after) several chills. Twenty-two hours after first chill and four hours before operation abdominal pain above pubes. Tenderness and spasm (more on right). Temperature fell to 98°, but rose at once. No distention. Pulse 120. No vomiting. Nausea. Leucocyte count, recorded as taken when pain complained of, 6000. No other count. Perforation eight inches from cæcum in ileum. Gas and turbid fluid in general abdominal cavity. General peritonitis not far advanced. Infection, pure typhoid bacillus. Perforation closed with silk, also two thin places enfolded. Death on fourth day, with symptoms of general peritonitis. Perforated coil of intestine was lying low down in pelvis. (Note locality of pain above pubes.) Perforation probably when pain was first noted. Operation reasonably soon. Typhoid infection, probably a virulent one. The general peritonitis was not far advanced at operation, yet was undeniably a general infection.

CASE 6. Devlin.—Male, aged twenty-four years, white. Drs. F. H. Williams and Munro. Boston City Hospital, November, 1899. Perforation and local abscess formation, with no diagnostic symptoms, followed by general peritonitis with severe symptoms. Death. Severe course. Widal negative. Rose spots. Large spleen. No complications. In fourth week, twenty-sixth day, operation. Ether. Time (?). Incision, right iliac. Irrigation. Drainage. Case stupid and sick. Fever high. No abdominal complaints till special ones. Two severe intestinal hemorrhages on day before in A.M. and P.M., accompanied by hard chill and collapse. Very near death at this time. Unconscious twenty-four hours after this. Abdominal pain. Tenderness, mainly right iliac. Distention. Rigidity. No vomiting. Leucocytes, 13,200. Temperature (?). Operation twenty-eight hours after hemorrhage. Operation four hours after pain, etc. General peritonitis with cloudy fluid; pus and feces in left pelvis free. In right iliac region an abscess cavity walled off by fairly strong adhesions, filled with pus, blood, and feces—large ragged hole in ileum near cæcum. No cultures recorded. Perforation closed. Death in forty-eight hours from general peritonitis. No autopsy. This case was one of perforation and forming of a walled-off abscess with no symptoms complained of by a very stupid, sick man. Time of extension to a general peritoneal infection doubtful. No cultures from general peritoneal fluid as well as from local abscess were taken.

CASE 7. Marchiono.—Male, aged thirty years, white. Drs. Henry Jackson and Munro. Boston City Hospital, July, 1898. Perforation. Sudden onset. Peritoneal infection not known. Quick operation. Death. Mild case. Widal positive. Diazo (?). No complications. No abdominal complaints. In third week, twentieth day, operation. Ether. Time, one-

half hour. Incision, right iliac. Irrigation. Drainage. Ten A.M. pain complained of in abdomen, with no special tenderness, nothing localized. No spasm. Leucocyte count then 8640, not taken again (?), 1.30 P.M. severe pain and chill, collapse. Abdomen everywhere tender and rigid, but especially on right side. Fall of temperature recorded to 98°, rising soon to 105°. No vomiting. Operation eight hours after first pain, five hours after collapse. One perforation in ileum ten inches from cæcum. No free fluid. "No extensive signs of peritonitis." Perforation closed. No cultures recorded. Death in forty-eight hours without symptoms of peritonitis. Partial autopsy through wound. Slight macroscopic signs of general peritonitis, but no bacteriology. Cause of death (?). Infection not known. In this case quick operation after first symptoms. Beginning peritonitis.

CASE 8. Schick.—Male, aged sixteen years, white. Dr. Gannett and Dr. Mixter. Massachusetts General Hospital, August, 1897. Case of perforation. Symptoms of peritonitis Perforation probably took place some hours before first symptoms. Death. Severe course. Widal positive. Diazo positive. End of third week, twenty-first day. Operation. Ether. Time(?). Incision, median. Irrigation. Drainage, gauze. Albumin, a trace in urine. Mitral regurgitation. Compensated. White count on entrance 4000.

High temperature and great abdominal distention all the time in the hospital, but no pain till August 20th (the day before severe symptoms)—*i. e.*, twenty hours before operation sharp pain in the left iliac region. No white count. Temperature falling gradually to 99.4° the following evening. No record of close watch of case. Next A.M. severe symptoms. Very great pain. Great distention, "board-like abdomen, most tenderness left iliac," bad pulse, anxious facies, no vomiting. White count, 7300. Perforation eight inches from cæcum in ileum. Virulent general peritonitis, pus and feces. Intestines covered with fibrin. No cultures. ("Peritonitis of longer standing than twenty hours.") Death in fifty hours. Peritonitis, spreading from a local area of infection or from perforation which took place without being noted. Small leucocyte count, possibly due to extensive purulent peritonitis. No comparative counts except one at entrance.

CASE 9. Hanahan.—Male, aged twenty-seven years, white. Drs. Fitz and Beach. Massachusetts General Hospital, November, 1897. Perforation. General peritonitis. Operation. "Second perforation" or giving way of sutured area eight days after second operation. Death. Mild course. Widal positive. Diazo positive. First of third week. Operation. Ether. Time, thirty minutes. Incision, median. Irrigation. No drainage. Slight bronchitis. Trace of albumin and hyaline and granular casts in urine. Nothing pointing to abdomen save a little distention. No intestinal hemorrhages till after first operation. December 6th, distention and tenderness to right of umbilicus. Temperature rising, pulse steady, no white count then. Leucocytosis at entrance, November 27th, 14,100; November 29th, 14,200; December 8th, 16,000. December 7th, tenderness increasing and temperature rising. No white count. December 8th, gradually falling

temperature and great increase in tenderness and distention of abdomen. Liver dulness obliterated. White count, 16,000. General tenderness, pulse 130, temperature 104. No vomiting. No complaint of pain. Operation next day (December 9th), about sixty hours after first warnings and twenty-four hours after symptoms of general peritonitis. The infection was a slowly spreading one, the severe symptoms on December 8th were probably due to the general peritonitis. The condition on December 6th and 7th strongly suggests a pre-extravasation stage, but comparative blood-counts are not recorded. Operation certainly would have been justified by these symptoms of general peritonitis fully fifteen hours before it was actually performed. Perforation one-eighth inch in diameter, one inch from cæcum in ileum (Beach). Closed. Foul gas and fecal fluid in belly. Yellow fibrin on intestines. No bacteriology. Did well after operation save for the continuation of typhoid temperature, averaging 102°, and three or four moderate intestinal hemorrhages. Some distention. Eight days after first operation pain all over belly, followed in three hours by collapse. Second operation: found large necrotic area and ragged hole in the cæcum, which was, for a great space around ulcer, soft and gangrenous—"shows patches of necrosis." Peritoneal cavity contained much dark fluid, feces and blood. Died five hours after. Autopsy: Much foul fluid in the peritoneal cavity. Many ulcers in last three feet of ileum and in ascending colon. In cæcum large necrotic areas, two small perforations, and two ragged large openings. In ileum no ulcer through to peritoneal coat, and no sutures found. Although this case has been considered a case of second perforation after recovery from the first perforation, the facts do not permit this view of it. The first perforation was said to be one inch from the cæcum, the second operation and the autopsy found great necrotic softening and ragged holes in the cæcum, and the autopsy found no ulcers in the ileum which were through to the peritoneal coat, and no trace of the silk sutures. The localities are practically coincident. It seems just to add that the case did well after the first operation until the extensive necrotic changes in the cæcum involving the sutured area caused giving way of sutures and second extravasation. Certainly eight days is too short a time in which a sutured ulcer could heal and vanish, and the silk sutures would not have disappeared.

CASE 10. Hoyt.—Male, aged nineteen years, white. Drs. F. C. Shattuck and C. B. Porter. Massachusetts General Hospital, October, 1896. Perforation. General peritonitis. No full study of early and warning symptoms recorded. Death. Mild course. No Widal test made. Diazo. No complications. No abdominal complaints. Thirteenth day, last of second week, operation. Ether. Time (?). Incision, median. No irrigation. Wiping. Gauze drains. No hemorrhages. Uneventful till October 26th. Pain in abdomen growing steadily worse. No collapse, no fall in temperature then. Pain steadily increasing. Legs drawn up. No records of any examination for spasm, etc., but records of morphine given. No white count. Eight hours after pain first noted symptoms of general peritonitis. Pulse 112,

sweating, temperature down somewhat, pinched face, belly rigid, tenderness general. Liver dulness not obscured. No vomiting. White count 14,700. Operation eleven hours after first symptoms. Perforation in ileum "near cæcum." This is called in record "a sloughing area from which gas was escaping, but no fecal matter." General peritonitis, sero-turbid fluid of fecal odor. No bacteriology. Perforation infolded with two rows of sutures. Death in thirty-six hours after great distention with obstinate vomiting. The autopsy raises a speculation as to the cause of death—whether due to obstruction from too much infolding of intestines by the two rows of sutures. The lumen of intestine at the point of suture admitted the little finger tip, but was obstructed by a hard impacted mass of feces. Whites at entrance, 6500. Eight hours after first pain, 14,700.

Case 11. Bresnahan.—Female, aged forty years, white. Dr. C. A. Porter and Dr. Thompson. St. Elizabeth's Hospital, August, 1899. Perforation. Definite early symptoms, which were not considered important. Operation six hours after severe symptoms. Death. Mild type and course. No Widal test made. No Diazo. Rose spots, etc. No complications. No abdominal complaints. In third week, operation. Ether. Thirty-five minutes. Incision, right. No second incision. Irrigation. Drained with gauze. Uneventful case. No intestinal hemorrhages. Twenty hours before operation pain in abdomen with some tenderness. No white count. No examination through the day. Six and one-half hours before operation pain severe, pulse 135. Three and one-half hours before operation—*i. e.*, sixteen and one-half hours after first complaint of pain—symptoms of collapse (general peritonitis). Temperature 106°. Muscle spasm and tenderness in right iliac region. No vomiting. Leucocytes, 8000. One perforation six inches from cæcum in ileum. V-shaped resection, silk sutures, one thin place inverted. General peritonitis. Free fluid of fecal odor. Injected intestines, with fibrin flakes. No cultures taken. Infection unknown. Death thirty-seven hours after. Partial autopsy through wound. Existence of other perforations unknown. Cause of death, peritoneal infection. Beginning infection probably when first pain, twenty hours before operation. No importance attached to early symptoms. Severe symptoms due to general peritoneal infection.

Case 12. McDonald.—Female, aged twenty-six years, white. Drs. Buckingham and Munro. Boston City Hospital, September, 1899. Case of perforation with excessive general peritonitis. Perforation and peritonitis much earlier than diagnosed. No symptoms save of general peritonitis. Death. Severe course. Widal positive. Diazo (?). No complications. No abdominal complaint. First of fifth week, thirtieth day, operation. Ether. Time of operation (?). Incision (?). Entered the Boston City Hospital in the fourth week. Two intestinal hemorrhages five days before "perforation." After these very sick, stupid. Pulse and temperature high. Some abdominal distention. No abdominal pain until the morning of September 18th, then pain and tenderness, requiring morphine. Four hours after this

great distention, general tenderness, chill, collapse, poor pulse, temperature fell to normal, but began at once to rise. No vomiting. Leucocytes, 3800 (note, general peritonitis with excess of fluid). No other count recorded, and no time of this given. Operation six hours after pain, two after collapse. Case "moribund" at operation. Perforation site not recorded. "Excessive general peritonitis, evidently of long standing; appearance of intestines and abdominal cavity showed general peritonitis of much longer standing than six hours" (Munro). No bacteriology. Death on operating-table. No post-mortem. This case was "stupid" and sick, and illustrates that perforation and general peritonitis may be gradual, and in a sick and stupid patient unnoticed until extreme septic infection.

CASE 13. Starnar.—Male, aged twenty-five years, white. Drs. Gannet and C. B. Porter. Massachusetts General Hospital, October, 1899. Perforation gradual. General peritonitis of long duration No very definite diagnostic symptoms. Death in two hours. Mild case. Widal positive. Diazo positive. No complications. First of fourth week or end of third. Operation. Ether. Time, one and one-half hours. Incision, median. Irrigation. No drainage. In the hospital ten days before operation. Abdomen distended most of the time, but no pain. Patient dull and stupid. Temperature high, pulse good. 4 A.M. intense pain, abdominal distention. No examination. 8 A.M., September 13th, sudden vomiting. No pain complained of, but abdomen much distended and knees drawn up, face anxious, general rigidity, abdominal and general tenderness. No fall of temperature recorded. White count, 8.30 A.M., 5400; 10 A.M., 4400; 2 P.M., 6300. Operation twelve hours after first pain. General peritonitis, cloudy fluid, gas in large amounts. Intestines much injected, distended, covered with fibrin. Perforation just above ileo-cæcal valve in ileum, "pin-head," closed. No culture. "Condition on leaving table very bad." Death in two hours. No autopsy.

CASE 14. McKenna.—Male, aged thirty-eight years, white. Drs. George B. Shattuck and F. B. Lund. Boston City Hospital, December, 1898. Perforation. General peritonitis. Definite warning symptoms. Death. Severe course. Widal positive. Diazo (?). No complications. No abdominal complaints. End of third week, twenty-first day. Ether. Time (?). First incision in right iliac, second in left. Irrigation. Drainage, gauze and tubes. 7 P.M. of the day before operation general abdominal pain, also pain in rectum and bladder. General abdominal tenderness and rigidity. No change in pulse and temperature. Leucocyte count, 10,000. Query as to why this was not repeated. No record of any observation of case till next day. The next morning (twelve hours after warning) symptoms of peritonitis recorded, viz.: Distention, anxious facies, vomiting, no fall of temperature, pulse rising to 120. Operation fifteen hours after first symptom. Perforation in ileum one foot from cæcum. Closed. Seropurulent general peritonitis, pus, and feces, fibrin. Infection, colon bacillus and other bacteria. Death in forty-two hours. Autopsy showed general peritonitis. No other perforations. Beginning of infection when first pain, fifteen hours

before operation. Definite warning. No record of case for twelve hours. Leucocyte count day before, when suggestive symptoms appeared.

CASE 15. Mahr.—Male, aged thirty years, white. Drs. Bowditch and Watson. Boston City Hospital, February, 1898. Perforations. General peritonitis. Early symptoms definite. Operation delayed forty-eight hours. Death. Mild course. No Widal. No diazo. Post-mortem proof. End of third week, operation. Ether. Time (?). Incision, median, and two counter incisions in flanks. Irrigation. Drainage-tubes and gauze. No special complications. Temperature normal for two days. No abdominal complaints till last. September 15th, A.M., vomited and complained of sudden pain, first in epigastrium, then all over abdomen and shooting into testicle. Tenderness in abdomen, general but most marked in right lower region and in epigastrium. "Shock not marked." Temperature rose from normal to 102°. Pulse 150. In a few hours rigidity of abdomen and tympanites. Leucocytes on September 15th, 31,550; next day, 17,000 to 23,000 (September 16th). In spite of these marked warning symptoms no operation for forty-eight hours. Then symptoms of fatal peritonitis, case nearly moribund, temperature subnormal, cold extremities, marked prostration, cyanosis, marked distention and rigidity. Operation found perforation in ileum near cæcum size of "split pea." Found general peritonitis, pus, fecal fluid, dirty-gray lymph, coils adherent, pus, pelvis full of turbid fluid, perforated coil fastened in abdomen wound. Infection: Colon bacillus and great variety of other bacteria (?). Death in six hours. Autopsy: Numerous typhoid ulcers in lower ileum. A second perforation (pin-point) close to valve. General peritonitis.

A repeated white count in this might have contributed much to the knowledge of a falling count in peritonitis.

CASE 16. Scappacci.—Male, aged nineteen years, white. Drs. Cutler and Eliot. Massachusetts General Hospital, June, 1899. General peritoneal infection from a necrosed and gangrenous patch over an ulcer. Threatened perforation. Definite warning symptoms of infection. Recovered. Mild course. Widal positive. No complications. No abdominal complaints. Last of second week, operation. Ether. Time (?). Incision, median. No irrigation, but wiping. Gauze drainage. Uneventful till June 4th, then pain in lower abdomen with general tenderness. Leucocytes June 2d, 6900; June 4th, 8000. No complaints or examination recorded for June 5th. June 6th, severe pain, abdomen tender and rigid, but more on right side; tympany, anxious facies, pulse 120, fall of temperature. Leucocytes, 12,200. No vomiting. Operation two days after first abdominal pain. Four hours after, symptoms severe. Four feet from cæcum a necrotic patch of peritoneum, the base of intestinal ulcer. General peritonitis, seroturbid, purulent fluid and fibrin flakes. Intestines injected, with green fibrin patches occasional. No cultures. Patch inverted. Recovery after relapse of typhoid. Infection not determined. A case of peritoneal infection from ulcer not yet perforated. Symptoms of perforation all present. Infection probably nonvirulent (?). Compare Case 21.

CASE 17. Bloom.—Male, aged forty-five years, white. Dr. Brooks. Massachusetts General Hospital, September, 1898. Extensive general peritonitis from perforation in walking typhoid. Infection not determined. Recovery. Widal positive. Ambulatory case. In second week, operation. Ether. Time (?). Incision, right iliac. Irrigation. Drainage, gauze. Case of typhoid as shown by Widal and by finding of typical ulcer indurations in ileum. Had been sick for a week or ten days with pains in abdomen. Up and about, out of bed most of time. (Walking typhoid.) Brought to accident-room 3 A.M. in bad condition. (Temperature 103.4°, pulse 134, respiration 60.) History of pain in region of appendix severe for two days, with nausea. Operation found brown, purulent fluid in general peritoneal cavity, with no odor; portions of small intestine covered with hemorrhagic spots "size head of tack." Perforation found one foot from cæcum. "Indurated area size of quarter, in centre of which pin-point opening." The appendix removed, incidentally, for old thickening. No active process in it. Perforation took place two days at least (?) before entrance. No white count. Recovered. No return of typhoid state, though Widal positive after operation. Discharged, well, in six weeks. No bacteriology.

CASE 18. McCarron.—Male, aged thirty years, white. Drs. Bowditch and Thorndike. Boston City Hospital, October, 1899. Perforation. Beginning general peritonitis. Operation eight hours after first symptoms. Death. Mild course. Widal positive. Diazo (?). No abdominal complaints. In the fifth week, thirty-third day, operation. Ether. Time (?). Incision, right iliac. Irrigation. Drainage-tubes and gauze. Cardiac murmur, systolic, not affecting compensation. No other complications. Early warning symptoms: 2 A.M., sudden, sharp pain in right iliac region. No fall of temperature, good pulse. Vomited. No blood count in this case. 7 A.M. (five hours after) severe symptoms. General severe abdominal pains and rigidity, especially right iliac. Pulse 120. Vomiting. Operation eight hours after first pain. Operation three hours after severe symptoms. Perforation in ileum three feet from cæcum. Perforation closed with silk. Straw-colored fluid and fecal matter in abdominal cavity. Intestines injected and fibrin flaked—*i. e.*, beginning general peritonitis. No cultures recorded. Death eighteen hours after. No autopsy. This case perforated eight hours before operation, when pain noted. If the case had been carefully watched with hourly blood-counts between the hours of 2 A.M. and 7 A.M. operation possibly could have been decided on three or four hours sooner. Severe symptoms at 7 A.M. due to general spreading infection.

CASE 19. Ellam.—Female, aged twenty-one years, white. Drs. Townsend and Burrell. Children's Hospital, October, 1899. General peritonitis. No perforation found. Symptoms of perforation or of peritonitis. Warning pain sudden and not reported. Death. Moderately severe. Widal positive. No complications. No abdominal complaints. Fifth week, thirtieth day, incision, right iliac region. Irrigation. Gauze and tube drainage. Intestinal hemorrhages daily from three days preceding severe symptoms. No abdominal pain with them. Sudden sharp abdominal pain

in the middle of the night; no examination. At 9 A.M. (eight hours after) severe pain, abdominal tenderness, and resistance, marked in right upper quadrant, slight distention. No leucocyte count recorded. No vomiting. Pulse 130. No fall in temperature noted, but rise to 104° at 9 A.M. May have fallen in the night. Operation eleven and one-half hours after pain. General peritonitis. Injected fibrin flaked intestines. No perforation found. "Thin place," but not necrosed; turned in. "Condition forbade search" for cause of peritonitis. No bacteriology. Death in twelve hours. No autopsy. This case could have been operated sooner. Severe symptoms came suddenly and were not reported for seven or eight hours.

CASE 20. Buckley.—Male, aged thirty-four years, white. Drs. Jackson and Munro. Boston City Hospital, September, 1899. Signs suggestive of perforation in third week. Very sick after this. Perforations in ninth week. General peritonitis. Early warning symptoms. Death. Severe course. No Widal. No diazo. Rose spots. Cardiac enlargement. Systolic murmur. In ninth week, fifty-ninth day, operation. Ether. Time (?). Two incisions: first, median; second, right flank. Irrigation. Drainage, gauze and tube. In the third week, while pulse and temperature were high, sudden fall of temperature. Collapse. Distended abdomen. Operation advised and refused. Leucocyte count then 6800. No other count recorded. From this attack very sick until ninth week. Abdomen distended. Pulse and temperature high. One small intestinal hemorrhage in fourth week. Twenty-four hours before operation abdominal pain, especially on left side. Pulse and temperature rising still higher. Twelve to fifteen hours after pain general and severe. Vomiting. Temperature subnormal. Two perforations in ileum three inches apart. (Where?) Also in ileum (site?). "Recent scar," "possibly healed perforation of third week." Perforations closed. General peritonitis, cloudy fluid with fibrin flakes. Infection, colon bacillus. Death ten days after. No autopsy. A frequent leucocyte count would have been very valuable.

CASE 21. Powell.—Male, aged twenty-seven years, white. Drs. Ames and Munro. Boston City Hospital, September, 1899. No perforation. General peritonitis from ruptured mesenteric glands. Symptoms of perforation exactly simulated. Infection, pure typhoid bacillus. Death. Mild course. Widal positive. Diazo (?). No complications. No abdominal complaints. Last of third week, twenty-first day, operation. Ether. Time (?). Incision, median. Irrigation. Drainage. Pain, abdominal, more on left side at 11 P.M. This required morphine. No further record till 7.30 A.M. (eight and one-half hours later), when collapse, anxious facies, tympanites, general abdominal tenderness, and rigidity. Temperature rising. (Temperature had been normal for twenty-four hours.) No vomiting. No leucocyte count. Operation twelve hours after pain. No perforations. Two suspicious thin places of inflamed peritoneum over ulcers. Seropurulent general peritonitis. Infection, pure typhoid bacillus. Death in twelve hours. Autopsy: No perforations. General peritonitis from two softened and ruptured mes-

enteric glands. This case strongly suggests the idea that symptoms of general peritonitis are identical with the "supposed symptoms" of perforation, and suggests the virulence of bacillus typhosus in peritonitis.

CASE 22. Sawyer.—Female, aged sixteen years, white. Drs. G. B. Shattuck and Watson. Boston City Hospital, December, 1897. No perforation. Nothing to account for symptoms of infection. Leucocyte count not taken. Recovered. Mild course. Widal positive. Diazo (?). No complications. No abdominal complaints. In sixth week, thirty-sixth day, operation. Ether. Time (?). Incision, right iliac. No irrigation. No drainage. Uneventful case. Temperature falling steadily. At no time especially sick. The afternoon before operation, severe abdominal pain and tenderness in right iliac. Temperature rising to 104°. Pain local in "lower abdomen," gradually increasing, not sudden. Next morning pain and tenderness general, but more on right side. Temperature 102°, pulse 128. No vomitin. Abdominal muscles rigid. No distention. No leucocyte count. "Absence of marked shock." Operation seventeen to eighteen hours after first symptoms. No perforations. No peritonitis. Appendix not actively inflamed, but bound by old adhesions; removed. Recovery uneventful. Important case from diagnostic side. Pain, tenderness, rigidity, rise in temperature and pulse. No great shock. No vomiting. The leucocyte count is all important, but is not recorded.

CASE 23. Eagles.—Female, aged twenty years, white. Drs. Vickery and Mixter. Massachusetts General Hospital, August, 1898. No perforation found at operation. No cause for symptoms of perforation which were definite. Recovered. Moderately severe. Widal positive. Complications, cardiac and renal. Abdominal complaints frequent. Fourth week, operation. Ether. Time (?). Incision. No irrigation. No drainage. Moderately severe case. Complicated by mitral regurgitation, with poor compensation and by acute renal congestion. Both cardiac and renal complications improved in hospital. Frequent complaints of moderate abdominal pain, which was due to retention of urine and relieved by catheter. Probably cystitis. Temperature lower and sitting up in bed in fourth week, when pain in abdomen complained of; white count at this time, 9200. Leucocyte count at entrance, 4200; twelve hours before operation, 9200, when pain first complained of; one hour before operation, 12,000. Twelve hours before operation, pain, abdominal tenderness, and spasm, mainly on the right side; slight distention; pulse 118. Temperature. No vomiting. Operation twenty-four hours after pain first noted. Nothing found. Recovery. Symptoms of gradual perforation, including some leucocytosis. No marked shock recorded. Query as to how to account for leucocyte count. Compare this case with Sawyer, Case 22. Same symptoms, but in Sawyer's case no leucocyte count. The comparative value of leucocyte count in this case is questionable.

CASE 24. Seile.—Male, aged twenty-seven years, white. Dr. Balch. Massachusetts General Hospital, September, 1897. Symptoms of peritonitis

of gradual onset. Operation found necrosed patch, but no macroscopic general peritonitis. No leucocyte count. No cultures. Death. Mild course. Widal positive. No complications. Fifth week, operation. Ether. Time (?). Incision, median. Irrigation. No drainage. Slight intestinal hemorrhages at intervals for three weeks before operation. Ten days before, abdominal distention, but no pain or rigidity. Temperature rising. Distention only transient, none two days before operation. September 25th, at noon, pulse 140, some sweating in the afternoon. Pain below and to left of umbilicus. Abdomen distended (spasm, vomiting, and white count not recorded). (Temperature not recorded). September 26th, picture of peritonitis, anxious face, pain, restlessness. Liver-dulness obliterated. Operation twenty-four hours after first symptoms. No perforation, one Peyer's patch, one and one-half feet from cæcum, threatening perforation, with fibrin area on intestine, "green, necrotic area," this inverted. No extravasation in peritoneal cavity. No bacteriology. Death in ten hours. Autopsy showed no general peritonitis. Only local necrotic patch. Death from typhoid.

CASE A. Eladed.—Male, aged fifteen years, white. Drs. Bowditch and Munro. 1899. Case of general peritonitis. No perforations. Gall-bladder infected with typhoid bacilli. Cause of peritonitis unknown. Sick case. Widal negative. Diazo negative. Large spleen. Sick for four weeks. Came into hospital with general peritonitis. "Nearly moribund at entrance" (Bowditch). Delirious; distended belly; distended, rigid muscles; temperature 104°; pulse 120. Leucocytes 5200 (note purulent peritonitis of long standing). No symptoms of perforation. At operation for general peritonitis no perforations found. Gall-bladder opened, but no evidence of origin of peritonitis. Cultures of free peritoneal fluid, St. Albus. Cultures from gall-bladder, bacillus typhosus. Exploration only half satisfactory (Munro). No anatomical evidence of typhoid found. Death in twenty-four hours. No autopsy. No conclusive proof that this was a case of general peritonitis during typhoid. Moribund case of general peritonitis, cause of which doubtful. Should not be counted with other cases.

CASE B. Collins.—Male, aged twenty-five years, white. Drs. Jackson and Gavin. Boston City Hospital, September, 1895. Case of general peritonitis. No evidence of typhoid fever. No Widal. No rose spots. No spleen. Case of no value. This case had general peritonitis, was operated on, and died. No reason to call it typhoid. No post-mortem. Leucocytes 32,000 before operation.

CASE C. James.—Male, aged (?). Dr. Munro. Boston City Hospital, 1895. Case of general peritonitis. No evidence of typhoid or of perforation. Case of no value. Case entered the Boston City Hospital with general peritonitis. Operated on and died. No cause for peritonitis found. No autopsy.

IDIOPATHIC PHLEGMONOUS GASTRITIS.

By FRANCIS P. KINNICUTT, M.D.,
OF NEW YORK.

PHLEGMONOUS or suppurative gastritis is so rare a disease, and the number of cases—including both the circumscribed and the diffuse forms—reported in the literature of the subject is so small, that the presentation of a specimen with the clinical history of the case may be of interest to the members of the Association.

The earliest description of the disease would seem to be in a communication by Verandaeus[1] in 1620. In the latter half of the seventeenth century and in the beginning of the eighteenth there are published observations by Borel,[2] 1656; Sand,[3] 1701; Vorwaltner,[4] and Bonet.[5] All of these observations describe the circumscribed form alone. Andral,[6] 1839, and Cruveilhier[7] appear first to have observed the diffuse form of purulent infiltration of the gastric walls. In their case only a fortunate accident led to incisions into the stomach walls, which revealed a diffuse submucous suppurative inflammation. Since 1860 papers both on the circumscribed and diffuse forms have been published by Raynaud,[8] Auvray,[9] Leube,[10] Hun,[11] Glax,[12] Lowenstein,[13] Oser,[14] Reinking,[15] Kelynack,[16] among others; and, finally, a very admirable monograph by Leith,[17] of Edinburgh, in 1896.

Leith[17] has been able to collect only fifty-one positive cases of the diffuse form in the entire literature of the subject, and the total number of cases both of the diffuse and the circumscribed forms is given as eighty-five. For a very interesting discussion of the entire subject especially I would refer to Leith's[17] monograph.

The specimen which I present is an exquisite example of the primary diffuse form of the disease. A single other instance of a similar form came under my observation many years ago in the

wards of Bellevue Hospital, in which the true lesion was only demonstrated at autopsy.

Clinical History. M. L., male, aged forty-one years; plumber. Admitted to the Presbyterian Hospital, April 10, 1900. Service of Dr. Kinnicutt. *Family history,* unimportant. *Previous history.* There is no history of syphilis. An alcoholic habit has existed for many years. The patient states that he has never suffered from gastric disturbances except at times of excessive drinking, and has enjoyed excellent health.

Present Illness. Five days before admission to the hospital, after drinking to excess and after a hearty meal, he suddenly began to vomit. The vomited matter consisted at first of the food in the stomach, and later of a brownish fluid. Vomiting occurred frequently during the four subsequent days, irrespective of the ingestion of food, which was only fluid in character. There was never any blood in the vomited matter. There was moderate diarrhœa for the first three days, and then no further movement of the bowels previous to admission. Blood was not present in the stools. With the onset of the vomiting he suffered from pain located in the epigastrium and in the lower abdomen. The pain was acute and more or less constant for the first three days. For the two days previous to admission he was comparatively free from suffering. With the occurrence of the first symptoms of his illness there was a feeling of chilliness, but no distinct chill.

Examination on Admission. The patient is a large, muscular man, well nourished, and not anæmic in appearance. The tongue is very dry and moderately coated. The respirations are shallow, 48; the pulse is full, a little tense, 108; temperature (rectal), 101°. The patient is very restless, anxious, and obviously very ill.

Heart: The apex is in the fifth space, in the mid-clavicular line. The left limit of cardiac dulness in the fifth space corresponds with the apex impulse. No murmurs are appreciable.

Lungs: Negative beyond slight dulness at both bases and moderate subcrepitation over these areas.

Liver: Percusses from the sixth rib to the costal arch in the mid-clavicular line; edge not palpable.

Abdomen: Is moderately distended, with considerable rigidity of the abdominal walls, most marked in the upper half. There is

moderate sensitiveness on deep palpation and slight on gentle palpation, and this sign is not obtained uniformly over the abdomen, but at several points, being most marked over the epigastrium and right hypochondrium. It has been noted that the liver-dulness is not obliterated, but fully reaches the costal arch in the midclavicular line. Over the liver region just above the costal arch, and also over the left hypochondrium in the anterior axillary line, scanty crepitation is heard, and is believed to indicate an involvement of the peritoneum. Signs of free fluid in the peritoneal cavity are not obtained. Abdominal respiratory movement is present, but diminished. The urine is free from albumin and sugar; specific gravity, 1.025. It contains a few hyaline and granular casts.

Lavage was immediately given, and a yellowish-brown fluid, without odor, considerably larger in amount than that introduced, was returned by siphonage.

A general peritonitis was believed to exist; the causative lesion was judged to be either an acute pancreatitis or a perforating ulcer of the duodenum.

On consultation with my colleague, Dr. McBurney, an exploratory laparotomy in the pyloric region was decided upon. The patient's condition, however, so rapidly became worse, the heart very suddenly failing, that surgical interference was not deemed advisable.

Death occurred sixteen hours after admission. Large quantities of a yellowish-brown fluid were repeatedly vomited during this period. The patient suffered little pain, and there were no further symptoms other than those of collapse.

Autopsy. Anatomical diagnosis: Diffuse suppurative gastritis; general peritonitis.

Frame large. Adipose considerable. Muscle fairly developed. Heart: Weight, 12½ ounces. Pericardium, normal; valves, normal; muscle, normal.

Lungs: Moderately congested at bases; a few old adhesions of pleuræ.

Liver: Weight, 73½ ounces; firm in consistence; surface deeply congested in places; for the most part pale; on section, pale; otherwise normal in appearance; a few old adhesions present and some recent fibrin. Gall-bladder: Filled with pale brown, very viscid bile.

Spleen: Weight, 5¼ ounces; surface smooth; consistence soft; on section, coarsely mottled, pale, and dark red.

Pancreas: Normal in appearance and on section.

Adrenals: Normal in appearance and on section.

Kidneys: Left, weight 6½ ounces; capsule adherent, surface smooth; on section, normal in appearance. The right kidney is similar in weight and appearance to the left.

Ureters, bladder, prostate, and seminal vesicles normal.

Abdomen: The peritoneal cavity contains a moderate quantity of turbid fluid. There is a small amount of fibrinous exudate adhering to the surface of the peritoneum at various points. The omentum is adherent to the mesentery by firm, slender bands, across which hang some loops of small intestine.

Stomach: Normal in size; its walls are greatly thickened, extraordinarily so in the pyloric region; on section, the thickening is seen to be due to a purulent infiltration of the submucosa. At the pylorus and to a point three inches from it the thickness of the submucosa throughout the circumference of the walls is fully an inch. Elsewhere its thickness is a little less, and is very uniform. The process is sharply limited at the pyloric ring. Not so at the cardiac orifice, where it extends upward to a point about two inches from the orifice. The infiltration is of a yellowish-white color, and is firm and solid; only a little watery fluid exudes on firm pressure. It separates the mucous from the muscular coat with great distinctness, both of these coats standing out prominently on either side of it. The surface of the mucosa is uneven and, in places, greatly congested, especially near the cardiac end. The muscular coat is slightly swollen. On the posterior wall of the stomach, near the lesser curvature and three inches from the pylorus, there is a linear cicatrix, an inch and a quarter in length. At the lower end of the cicatrix there is a small area, necrotic in appearance.

Microscopical Report. (From the pathological laboratory of the hospital, by Dr. Berkeley.) Minute anatomy of the stomach wall: Note.—Tissue hardened in formalin and alcohol, mounted in celloidin, stained with the usual reagents.

The serous and subserous layers show irregular thickening and infiltration with round cells. The endothelial covering is in most places entirely lost.

Muscular coat: The fibres of the muscular layer are swollen and much distorted. The connective framework is everywhere crowded with leucocytes. These leucocytes are of unusual size, are mainly mononuclear, and the nuclei are, as a rule, round, more rarely crescentic or irregular. There are a few apparently polynuclear forms. Some of these have penetrated even between the individual muscular strands.

Submucosa: This layer is enormously thickened, measuring in certain places three-fourths of an inch even in the hardened section. It has evidently been the main seat of the bacterial infection. Its fibres are widely separated by quantities of fibrin, leucocytes, lymphocytes, and complete strata of bacteria. The violence of the inflammation has caused extensive areas of partial or complete necrosis; in these only the faintest outlines of cells and fibrils are still distinguishable. The lymphatics are here and there gorged with microbes. Between the submucosa and the mucosa proper the necrotic spaces are less numerous, but vast numbers of lymphocytes (many more than those normally present) are to be found. The muscularis mucosæ is generally in place, and unexpectedly enough seems to have participated in the pathological process less than any other layer of the entire stomach.

Mucosa: This is preserved in a few places. Here the peptic glands are in various states of inflammation and degeneration. The nuclei of the glandular cells stain everywhere ill or not at all. The protoplasm is markedly granular. In other portions the mucosa is eroded, or necrotic, or quite absent. Sections made through the necrotic part of the old cicatrix referred to in the description of the macroscopical appearances (by Dr. Kinnicutt) show that at one point the infiltrated submucosa is completely exposed by a deep erosion in the inflamed and necrotic mucosa. Whether or not this was the point of original pyogenic infection does not, of course, admit of demonstration; such a hypothesis, however, seems reasonable.

In respect of the anatomical extent of the inflammation, it is rather strange that while the phlegmonous swelling is perfectly and clearly delimited on the left by the pyloric valve of the stomach, the lower (cardiac) end of the gullet has not escaped; the latter shows for some distance upward practically the same changes

found in the stomach wall, viz., swelling, softening, intense cellular infiltration, and a countless number of micro-organisms. Through the stomach itself the infiltration is universal, and the degree of swelling is high everywhere.

The bacteriological examination shows the practically universal presence of a streptococcus. It is most abundant in the connective tissue of the submucosa and muscularis. Some of the individual chains are quite long, being made up of eight or ten members. Most are shorter. Contrary to the classic descriptions, few or no cocci are to be found inside the leucocytes. The strata mentioned above are made up almost entirely of these chain cocci. The lymphatics contain not so many cocci as bacilli The latter are long, with deeply stained ends (spores?). They are possibly of post-mortem origin, inasmuch as they are abundant in the superficial vessels. No cultures were made from the stomach, but films made from the exudate on the cut surface show that the streptococcus is the prevailing pathogenic organism.

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DISCUSSION.

DR. WELCH: I recall a case of diffuse phlegmonous gastritis which I examined at autopsy several years ago at Bellevue Hospital, New York. The patient was a man beyond middle life, with a history of chronic alcoholism. Abdominal pain, vomiting, and fever were among the symptoms, the diagnosis during life being acute peritonitis. The walls of the stomach were nearly one centimetre in thickness and were diffusely affected, although the pyloric region was the most thickened. The thickening was most marked in the submucosa, which presented a yellowish-white, rather firm appearance. There was no tumor or large ulceration, but small drops of pus could be squeezed in many places from the surface of the mucosa as through a sieve, and also from the incised wall of the stomach. There was diffuse seropurulent peritonitis.

The microscope showed an immense diffuse infiltration of the submucous coat with leucocytes, chiefly polymorphonuclear. In scattered foci were small submucous abscesses. Lines of pus cells extended up between the gastric tubules and opened upon the free surface. The accumulation of pus cells was most abundant in the inner layers of the submucosa near the muscularis mucosæ, but the outer layers were also infiltrated, and strands of pus cells extended through the muscular coats, the intermuscular and subserous layers of connective tissue being considerably thickened by purulent infiltration. The peritonitis appeared to be secondary to the phlegmonous gastritis. I did not at the time of the autopsy examine for the presence of bacteria, but I have since done so, and have been able to discover in the microscopical section numerous streptococci.

Phlegmonous gastritis was described by Brinton under the peculiar name of "suppurative linitis," and I recall that in my student days we were expected to know about it under this latter designation.

DR. JANEWAY: I have met with three primary and two secondary cases. The first case was in a physician, and has been reported by Dr. Loomis. He was not a drinking man, but a hard-working inspector of the Board of Health of New York City. The second case was the one referred to by Dr. Kinnicutt, and the third I saw in consultation with the late Dr. E. A. Maxwell, of New York. In this case I was enabled to make a diagnosis of the condition by the development of the perigastritis after the irritating severe gastric symptoms. The two secondary cases followed sepsis, and were not so generally diffuse as this, but spots of suppurative gastritis were found.

STUDY OF A MUMMY AFFECTED WITH ANTERIOR POLIOMYELITIS.

By JOHN K. MITCHELL, M.D.,
OF PHILADELPHIA.

In the Archæological Museum of the University of Pennsylvania there is the skeleton of an Egyptian, of a period about 3700 years before Christ, which presents some problems of interest. Mr. Flinders Petrie found this mummy at Deshasheh, a village on the western edge of the plain, some eighty miles south of Cairo. Although the tomb had been rifled, the style of burial indicated sufficiently that the body was that of a man of the better class. The coffin is hewn out of a single great log of sycamore; in the end the rings of growth may still be counted with ease enough to determine the tree as not less than three hundred years old when it was fashioned. A straight stick about four feet in length and half an inch in diameter lay alongside the body, broken in three pieces. It was observed by Mr. Petrie that the man had one leg much shorter than the other, and he supposed the thigh to have been broken; but, as will be seen, there is no evidence of this.

The bones, which are exceedingly light and fragile from age, have been carefully articulated, and except for certain small losses of substance where they have crumbled away, are in good preservation, and their sizes and relations are readily studied.

The skeleton is that of a small male, the extreme height being 1.63 metre. Making allowance for flesh and cartilage, the subject in life could scarcely have exceeded 5 feet 5½ to 6 inches. That he was an old man is shown by the ossification of the rib cartilages, the obliteration of the sutures in the skull, and by the much-worn grinding surfaces of the remaining teeth. The general capacity of the skull, the square and well-formed jaw and facial angle all indicate

character and intellect, and confirm the belief suggested by the methods of burial and preservation, that the man belonged to the educated and wealthy governing or upper class. One notices at once that the left leg is considerably shorter than the right, and at first sight the femur of the left side seems heavier and thicker than the right one. Measurement, however, makes it evident that the left femur's apparent greater circumference is only due to its shortening and to the strongly marked ridges at the site of the muscular attachments, which suggest that the muscles may have even been hypertrophied on that side. With this exception the left femur is imperfectly developed in all directions.

The left femur is 8.2 cm. shorter than the right, round the middle of its shaft it is 1.2 cm. less; the neck is 0.4 cm. less in circumference. Condyloid measurements could not be compared, as the left condyles are somewhat crumbled. The necks of the femora are the same length on both sides. There is no sign of fracture or injury to the bone of the left thigh. Only a very minute and practically negligible difference can be made between the bones of the lower leg on the two sides, not more than 0.5 cm., an amount of difference often exceeded in healthy limbs; but it should be said that though the shortening is very slight it is on the left side.

So far as can be told the bones of the feet are unaffected, but as the terminal phalanges have crumbled almost entirely away, nothing can be stated with certainty about them.

The pelvis is perfectly formed and the vertebræ present no sign of unequal or imperfect development, so that evidence is wanting of any compensatory curvature, such as might be expected in a patient who had come to old age with one leg three inches shorter than the other. These facts and the marked prominences for muscle attachment on the surface of the short thigh bone suggest that during life some means of compensating for the shortening must have been used, such as a high-soled shoe, or rather sandal, might afford, the additional weight of which perhaps aided in bringing about a certain degree of hypertrophy of the thigh muscles on the affected side. Moreover, the stick found in the coffin, as my friend, Dr. Edward Martin, who at my request remeasured the bones and examined them for evidence of injury, ingeniously suggested, is too long and slender to have served as a support, and must have been merely a balancing staff.

The impossibility of cross-examination of the patient on his early history leaves us free to conjecture as to the cause of the difficulty, but nothing seems so probable as that the defect of growth is due to an attack of poliomyelitis, perhaps even an intra-uterine one. It is certainly unusual, though not unheard of, that only one segment of a limb should be affected; but this disease is notoriously irregular in its distribution; for example, when it occurs in the arms it is sometimes limited to the upper, sometimes to the lower arm. Every one knows how constantly the anterior tibial muscles remain weak when other muscles make fair recovery from their palsy, insomuch that one is inclined to consider such a weakness as a sign indicative of infantile paralysis where the cause of a lameness is doubtful. Yet at this moment I am treating a patient in whom bilateral infantile paralysis of the anterior thigh muscles is present, while the anterior tibials on both sides are perfectly sound. No theory has been proposed which will account for the frequency with which these groups are picked out, nor, indeed, anyone which will adequately explain why the disease should affect only the anterior cornua. What is curious is that I cannot find in the dozen great works of reference which I have consulted in the effort to settle this small point, any categorical statement as to whether the growth of one bone alone may be affected and its attached muscles escape, or be affected with it and recover later. The subject is one for larger discussion and study—and I have been concerned with the presentation only of what is, if my supposition of the causation is correct, the earliest known case of infantile palsy, although Dr. Osler has hinted his opinion[1] that the lameness of Jonathan's son, Mephibosheth, was due to this trouble, an opinion founded, I fear, on even slenderer bases of fact than the one here expressed.

[1] See Osler's "Practice," Art. Infantile Palsy, and II Samuel, iv., 4.

A CASE OF MULTIPLE MYELOMA.

By JAMES H. WRIGHT, M.D.,
OF BOSTON.

(Plates I—III.)

(*From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.*)

Multiple myeloma may be defined as a primary neoplasm of the bone-marrow, affecting chiefly the sternum, the ribs, the vertebræ and the skull; the substance of the bone being more or less extensively replaced by the tumor tissue. The neoplasm may invade the neighboring soft parts by continuity of growth, but it probably never forms metastases, as do the common malignant tumors. The disease usually occurs in men in the latter half of life. Probably it has been confounded with osteomalacia in some cases.

The affection was first recognized and described as a definite pathological condition, in 1873, by J. von Rustizky,[1] who gave it the name of multiple myeloma. Since that time at least seventeen cases of multiple primary bone tumors, presenting the essential characteristics of multiple myeloma, have been reported. To this number should be added two previous cases, one reported by Bence-Jones[2] and Mackintyre[3] and one by Weber.[4]

From the great similarity of the lesions in these cases it might be expected that the histological characters of the neoplasms would be the same in all the cases. This, however, is not so. A great diversity exists in the results of the histological examinations of the cases in which such examinations have been made. The neoplasm has been called lymphosarcoma, myelogenous pseudoleukæmia, lymphadenoma,

[1] Deutsch. Zeitschrift f. Chirurg. 1873, Bd. iii., S. 162.
[2] Philosophical Transactions of the Royal Society, 1848.
[3] Medico-Chirurgical Transactions, 1850.
[4] Transactions of the Pathological Society, London, 1867.

hyperplasia of the marrow, vascular endothelioma, and different types, of sarcoma. Nearly all of the descriptions of the finer details of the cells are inadequate and unsatisfactory, so that it is impossible to determine whether any two of the cases are identical or not in their histological characteristics. In at least eight of the cases, however, the tumors were made up essentially of cells which were variously described as small round cells, or as lymphoid cells, or as cells like marrow cells, or as cells of round-cell sarcoma, or as round or polygonal cells, 1-2000 of an inch in diameter. The neoplasm in all these cases was probably one and the same in microscopical structure, and it is to this group that the case here reported probably belongs.

An interesting feature of the present case was that the urine contained albumose. The association of albumosuria with multiple myeloma and osteomalacia has been observed in a number of cases since Bence-Jones[1] discovered this substance in the urine of his case. The clinical importance of this fact has been emphasized by Dr. R. H. Fitz[2] in a paper in which the present case is referred to, and also by Drs. Bradshaw and Warrington in a recent paper.[3]

The case here reported was under the care of Dr. R. H. Fitz, who made the diagnosis of multiple myeloma from the presence of a tumor of the sternum, lesions in the ribs and from the albumosuria. The Röntgen rays proved of great service in recognizing the existence of lesions in the ribs.

The patient, a man fifty-four years of age, entered the Massachusetts General Hospital, February 24, 1898. About a year before entrance he had noticed for the first time a small tumor at about the level of the nipples. This had grown steadily in size. At times, especially at night, he had had pain in the axilla. This pain seemed to the patient to be connected with the tumor.

About four years previously he had noticed that at times he walked like a drunken man. Later he had to use a cane in order to walk. His feet felt numb, but the sense of touch and the muscular sense were retained. There never had been pains in the legs and never spells of severe vomiting. For some time he had had double vision,

[1] Loc. cit.

[2] Transactions of the Association of American Physicians, 1898. American Journal of the Medical Sciences, July, 1898.

[3] Transactions of the Royal Medical and Chirurgical Society, 1899.

loss of sexual power, and some incontinence of urine. He gave a fairly good history of syphilis.

At the time of admission, or shortly afterward, the following facts were noted: Pupils equal and react to light and accommodation. Slight strabismus of the right eye. In the sternal region at about the level of the nipples a rounded tumor, about four and one-half inches in greatest diameter, elevating the skin. This tumor has a smooth surface, is rather soft, and is slightly pulsating. In the left back near the middle of the vertebral column a small area of dulness about the size of the palm of the hand. In connection with the ribs at the back there are several tumor nodules.

Examination with the Röntgen rays showed changes in the fifth, sixth, seventh, eighth, eleventh, and twelfth ribs posteriorly on the left side, and in the seventh and eighth ribs on the right side between the angle of the scapula and the spine. The knee-jerks exaggerated. Pronounced ankle clonus. No disturbance of sensibility. No atrophy. Good muscular power.

Shoes worn at the toes and the outer side of the median line. No increase in the arm reflexes. No fever.

Urine examination: Albumose in abundance. Slight trace of serum albumin. Pus as sediment. Urea, 0.76 per cent.

Blood examination: Hæmoglobin, 60 per cent. Whites, 5000. Reds, 4,700,000.

During the next four months the condition of the patient remained practically stationary. The tumors of the ribs increased somewhat in size, but the tumor of the sternum did not. In the head, at the junction of the sagittal suture with the lambdoidal suture, a soft tumor the size of a filbert appeared. The urine continued to contain albumose, the analysis by Dr. Edward S. Wood, in March, showing 0.33 and 0.34 gramme in 100 ccm. of urine. In the same quantity of urine there was also 0.03 gramme of serum albumin.

After about four months the patient began to grow rapidly weak and to suffer much pain. Finally he became unconscious and died July 26, 1898.

The autopsy was performed twenty-two hours after death. An abstract of the autopsy records of the pathological laboratory is as follows:

The sternum in its inferior and median portions is much increased

in thickness, bulging externally to form a flattened, somewhat fluctuant tumor, about 9 cm. in diameter, beneath the soft tissues, and also bulging internally to form a lobulated tumor mass. A longitudinal section through the sternum shows the bony tissue, except at the extremities of the bone, almost entirely replaced by a tissue which is partly soft, mushy, grayish-red to dark-red in color, and partly moderately firm, whitish, and semitranslucent. In the superior mediastinum, and loosely attached to the sternum, are two or three soft tumors, the largest the size of a chestnut.

The sixth and eleventh ribs on the left side lose their continuity near the spinal column in a soft, mushy, red tissue, somewhat resembling red marrow. This tissue forms tumor masses beneath the pleura at these points, the largest being about the size of a hen's egg. The tenth rib on the right side and the eleventh rib on the left side present comminuted fractures. There are also callus-like thickenings on the seventh and eighth ribs on the left side, and on the fourth, seventh, and eighth ribs on the right side. The ribs in general seem more friable than normal.

The bodies of several of the dorsal vertebræ are found to contain larger and smaller soft, red masses of material like red marrow, filling cavities in the spongy bone. These masses are chestnut-sized in two or three instances.

In the approximate situation of the spinous processes and laminæ of the seventh and eleventh dorsal vertebræ are two masses of soft, mushy, grayish-red material, each less than a pigeon's egg in size. These have replaced the bony structure. The spinal cord is not pressed upon by these masses, and in hardened sections showed no definite lesions. The *dura mater* is more adherent than normal to the *pia mater* of the cord. The latter membrane, chiefly in the dorsal region, is thickened, and opaque whitish in color.

The marrow of the shaft of the right femur is yellow and oily.

In the occipital bone there is a circular defect about 3 cm. in diameter, filled with a soft grayish to dark-red tissue, and having a worm-eaten margin. In the frontal bone there is a similar defect filled with a similar red tissue.

Other conditions observed were: Bronchopneumonia and acute pleuritis of the inferior lobe of the right lung; œdema of lungs; senile degeneration of the kidneys; chronic interstitial orchitis.

HISTOLOGICAL EXAMINATION. Most of the material taken for histological purposes was hardened in Zenker's fluid. The remainder was hardened in Flemming's solution. Sections were cut in paraffin and in celloidin.

In preparing sections sufficiently thin for photographing at high magnifications the new Minot-Blake microtome[1] was used with great advantage. The sections were stained in various ways, eosin and Unna's alkaline methylene-blue solution, and fuchsin, either alone or in combination with aurantia, being found most useful.

The neoplasms in the sternum, ribs, vertebræ, and skull consist of one and the same tissue. This tissue is chiefly made up of small cells closely crowded together. Interspersed among these cells are rather numerous thin-walled bloodvessels, usually about the size of an ordinary capillary or a little larger. (Plate II., Figs. 4 and 5.) A few delicate fibrillæ are also present among the cells, but these are difficult to see, so that the tissue at the first glance seems to have no supporting framework for its cells except the thin-walled bloodvessels. These fibrillæ are best seen in sections hardened in Flemming's solution, where they appear as delicate strands of irregular course. (Plate II., Fig. 5.)

The cells of the tissue are, as a rule, circular in outline, and are somewhat variable in size. Most of the cells measure six to eight micra in diameter in the hardened section. They seem to have no cell membrane.

The nuclei are round or slightly oval in outline, and have a well-marked nuclear membrane. They vary somewhat in diameter, which is usually about one-half or two-thirds that of the cell. They are often situated eccentrically in the cell. A few are considerably larger than the average.

A striking characteristic of the nuclei is the presence of a variable number of intensely staining chromatin masses, of round or oval outline, continuous with the nuclear membrane and projecting from it into the interior of the nucleus. There is also a well-marked round globule of chromatin in the centre of the nucleus. This, in specimens stained with Unna's alkaline methylene-blue solution and eosin, may be sometimes observed to have a distinctly red color, if the blue stain-

[1] Francis Blake. "A New Microtome." Journal of the Boston Society of Medical Sciences, April, 1899.

ing be rather weak, while the nuclear membrane and the globules connected with it are stained blue.

A few cells have two nuclei and a very few three nuclei.

Karyomitosis is not seen in any of the cells, but a very few cells are seen having elongated, or hour-glass shaped, or dumb-bell shaped nuclei; and also cells having two nuclei connected together by a thin band or filament of chromatin, as well as cells having two nuclei, as above described. In view of the absence of nuclear figures these appearances suggest the idea that these cells multiplied by direct cell division. They might, however, be interpreted as the result of degenerative change.

The cytoplasm of the cells is homogeneous, and in some of the sections, after staining with eosin and Unna's alkaline solution of methylene-blue, it takes the bluish stain, while in others it takes a purplish tint, or it may be stained with the eosin alone, depending, apparently, on the relative intensity of the staining with the two dyes.

In many of the cells the cytoplasm at the central portion does not stain as deeply as the peripheral portion, so that it appears distinctly paler.

The tumor cells are very different from the majority of the cells of the red marrow. This is shown in Plate III., Figs. 6 and 7.

From the foregoing description, and from the photographs, it should be clear that these cells are, at least, closely related to the so-called "plasma cells" of Unna. Most of these cells have all the appearances of "plasma cells," except that the cytoplasm does not in all cases show a marked affinity for methylene-blue as does the typical "plasma cell." In the opinion of the writer these cells are essentially "plasma cells," or immediate descendants of them, and their deviations from the type of the parent cell are quite analogous to those seen in the cells of other neoplasms.

Most of the bloodvessels of the tissue are made up of endothelial cells only (Plate II., Fig. 5), but occasionally a few fibres of connective tissue may be seen just outside the endothelium. The majority of these vessels are like ordinary capillaries in size; some of them, however, are larger and of variable diameter, but none of them have any muscular tissue in their walls, which, at the most, have only a little connective tissue outside the endothelium.

In some sections red-blood corpuscles in considerable numbers are

present among the cells of the tissue. This is regarded either as the result of hemorrhage or as an artefact produced in removing the tissue from the body.

No necrosis of the cells is to be seen, nor any fatty degeneration.

As above stated, various ribs presented small thickenings and signs of fracture. Sections through five ribs at about the seat of these lesions were studied. All of these show more or less extensive replacement of the red marrow and of the bony trabeculæ of the *spongiosa*, as well as of the cortical bone, in places, by a tissue such as is described above. In one section this tissue has totally replaced the substance of the rib at that point, and has extended beyond its original limits, elevating the periosteum and the pleural tissue, thus forming one of the tumors noted in the continuity of the rib.

Another section shows a mass of the tumor tissue in the *spongiosa* in process of growing through the cortical bone. (Plate I., Fig. 1.) In various places in the *spongiosa* of the ribs, larger and smaller aggregations, or nodules, of tumor cells are present. They are not sharply defined from the surrounding marrow, but merge into it. (Plate I., Fig. 1.) Some of these are microscopic in size.

In thin sections of one of these ribs are seen cells identical with those of the tumors, scattered here and there singly and in groups through the marrow spaces and among the narrow cells.

The cortical bone is absent in many places, or it is represented by strips and islands of a granular, shrunken, abnormally staining bone. In only a few instances were osteoclasts seen associated with this evidently degenerate bone. In two of the sections some of the degenerate bone presents appearances clearly indicative of a new formation of bone at the margin.

One section showed a partly or completely healed fracture with formation of callus.

Sections of the bodies of several vertebræ show that these are more extensively infiltrated with the neoplasm than was apparent at the autopsy. In addition to a few tumor nodules, varying in diameter from a few millimetres to one centimetre or more, many smaller nodules are found scattered through the marrow. One of these is shown in Plate I., Fig. 2. They vary in size from one millimetre in diameter down to microscopic groups of cells. The nodules are not definitely separated from the surrounding marrow, but the tumor

cells at the margin infiltrate the spaces between the fat cells and take the place of the marrow cells. (Plate I., Fig. 3; Plate III., Fig. 6.) In thin paraffin sections cells like the tumor cells are found distributed here and there among the marrow cells. Plate III., Fig. 7, illustrates this. The tumor cells are here rather more numerous than usual.

From a study of the sections it seems clear that the tumor nodules have arisen by the aggregation of the tumor cells in the spaces between the fat cells, which spaces normally contain the vessels, marrow cells, and blood; then, by the further multiplication of the tumor cells, the fat cells and other cells and elements of the spongy bone are obliterated.

The occurrence of cells identical with the cells of the tumor scattered singly and in groups among the marrow cells, and the great likeness of these cells to "plasma cells," as above stated, suggests the idea that these cells, or "plasma cells," may be one of the varieties of the cells of the normal marrow. In order to test this idea specimens of presumably normal spongy bone of the sternum and vertebræ were examined in paraffin sections. As a result it was found that the red marrow does contain cells which are like those of this tumor, and apparently true "plasma cells," but they are present in smaller number than the similar or identical cells seen in the red marrow in this case. They are found singly, or several in the field of an oil-immersion lens. As a rule, they have to be sought for. In Plate III., Fig. 8, is shown a "plasma cell" in a section of normal red marrow. The general appearances of the cells of the marrow are shown, as also their differences from the "plasma cell" and from the tumor cells.

CONCLUSIONS. This case is one of multiple tumor formation, primary in the red bone-marrow, and widely distributed through the same.

The cells making up the bulk of the tumors are very like or identical with "plasma cells," which cells are a normal constituent of the red marrow. It, therefore, seems reasonable to think that the neoplasm, exclusive of its vessels and insignificant stroma, has arisen from an abnormal proliferation of these cells.

Under this view, this case of multiple myeloma is to be regarded as a neoplasm originating, not in the red-marrow cells collectively, but in only one of the varieties of the cells of the red marrow—*i. e.*, in the "plasma cells."

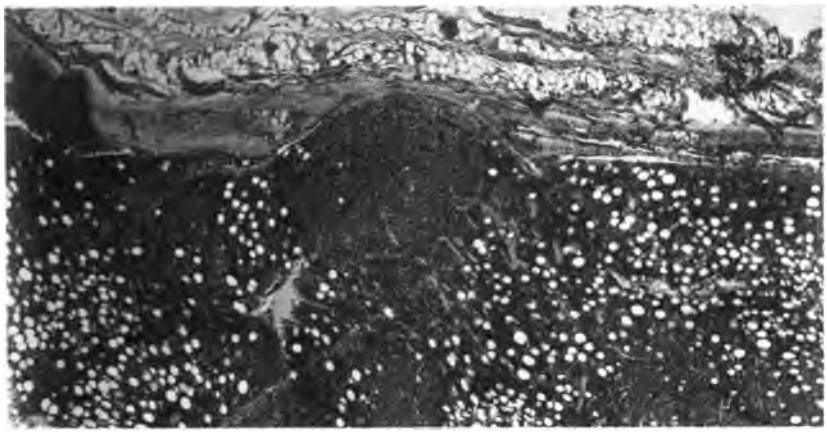


Fig. 1.

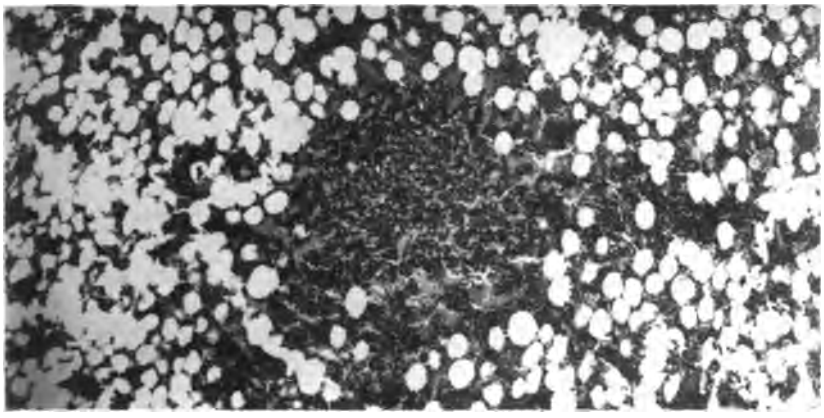


Fig. 2

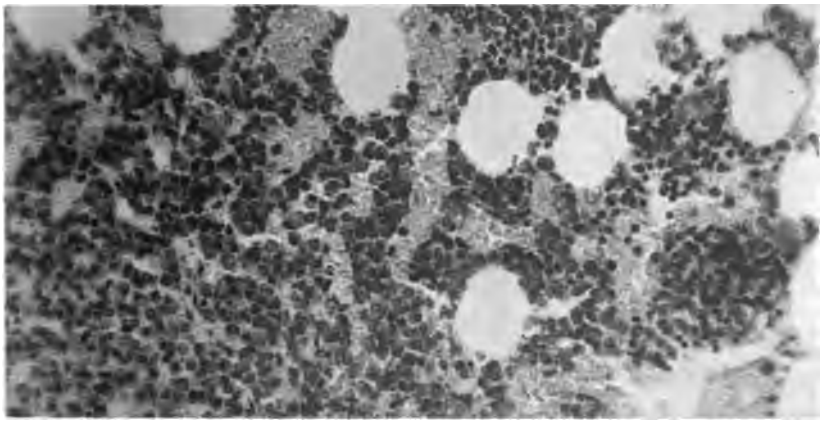


Fig. 3

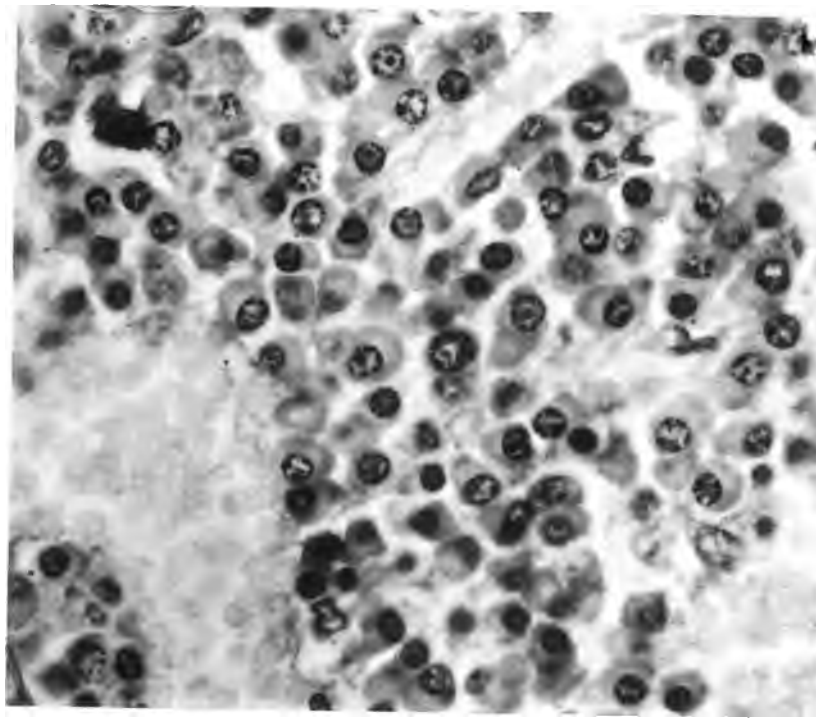
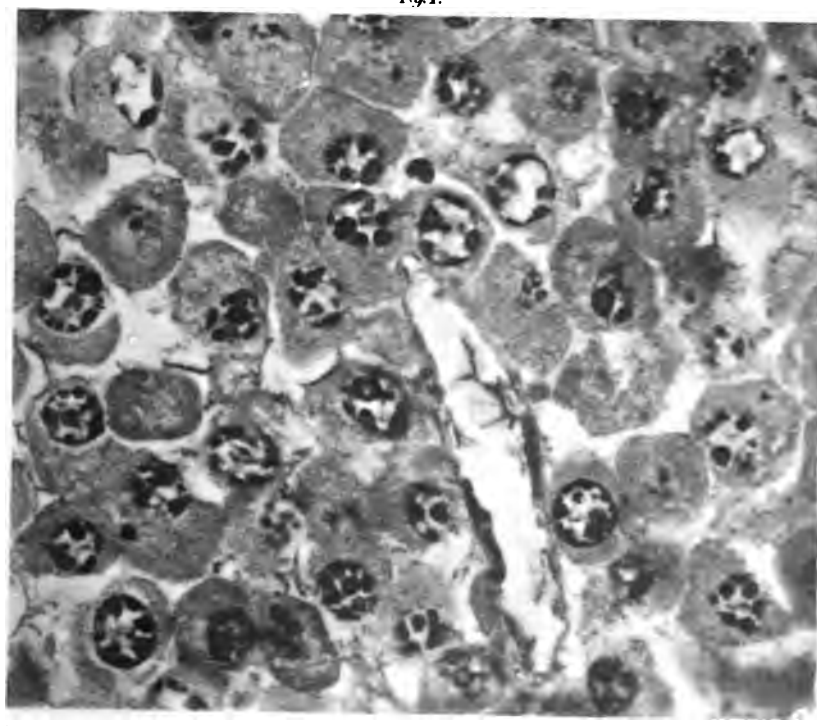


Fig. 4.



Heliotype Co. Boston.

Fig. 5

J. H. Wright.

Multiple Myelo

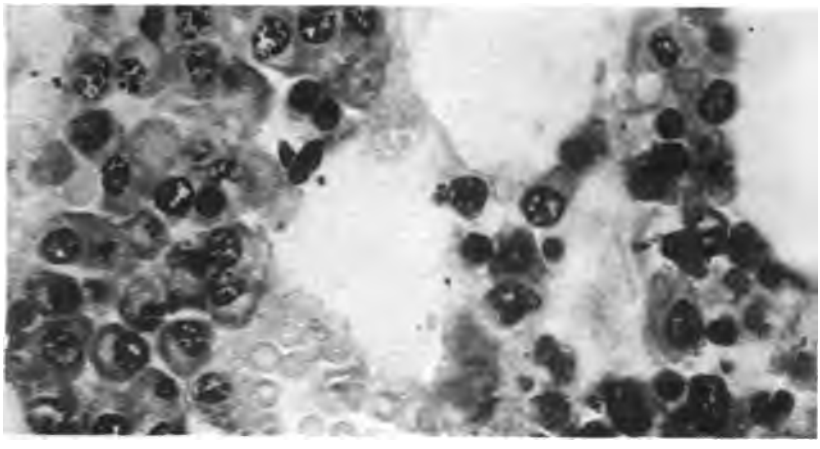


Fig. 6.

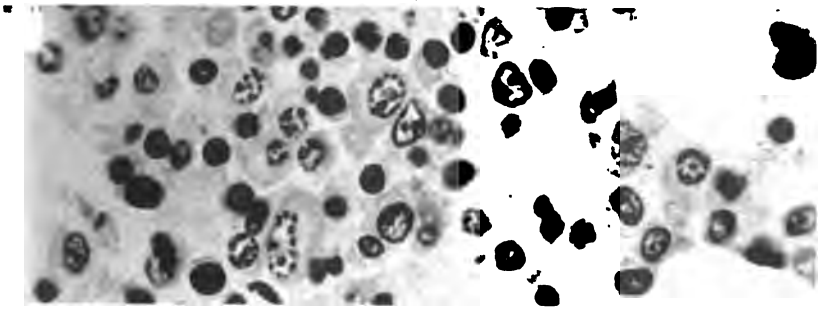


Fig. 7.

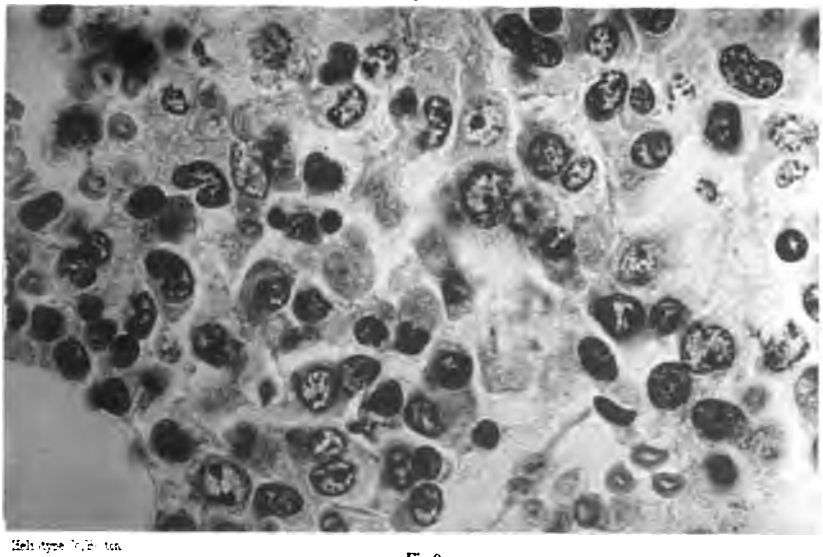


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Fig. 8.

DESCRIPTION OF THE PLATES.

PLATE I.

FIG. 1.—Section through the cortex and part of the spongiosa of a rib. The cortical bone is seen invaded by the growth. In two or three places in the spongiosa the narrow tissue is replaced by areas of tumor tissue.

FIG. 2.—Section of the spongiosa of a vertebral body. In the centre of the figure a small tumor nodule.

FIG. 3.—Section through a small portion of the body of a vertebra. A portion of a small tumor nodule and the adjacent marrow tissue is shown.

PLATE II.

FIG. 4.—Section of a portion of a small tumor in the body of a vertebra. The character of the cells and the general appearances of the tumor tissue are shown. × 1000.

FIG. 5.—Section through a part of the tumor of the sternum. Magnification 1500, approximately.

PLATE III.

FIG. 6.—From a section of the spongiosa of a vertebral body. An aggregation of tumor cells is seen in the left of the figure. On the right are seen the usual marrow cells between the fat cells. × 1000.

FIG. 7.—Section of spongiosa of vertebral body, showing tumor cells scattered among the marrow cells. × 1000.

FIG. 8.—Section of normal spongy bone containing normal red marrow. To the left of the centre of the figure is a "plasma cell." The general appearances of the marrow cells are shown. × 1000.

The photographs were prepared with the assistance of Mr. L. S. Brown, in the Laboratory of the Massachusetts General Hospital.

TREATMENT OF THE "CLINICAL TYPES" OF THE URIC-ACID DIATHESIS.

By I. N. DANFORTH, A.M., M.D.,
OF CHICAGO.

At the meeting of this Association in May, 1899, I had the honor to present a paper on the "Clinical Types of the Uric-acid Diathesis," in which I described three different types of that diathesis, as follows: (*a*) The plethoric type. (*b*) The neurotic type. (*c*) The anæmic type; illustrating each type by typical cases.

Toward the end of my paper I said: "It is not the purpose of this paper to treat at length or in detail of the therapeutics and dietetics of lithæmia, as I propose relating the result of my experience on a future occasion." It is the object of the present paper to carry out the purpose then announced, and ask attention, in considerable detail, to the treatment, dietary, and general management of the several types of lithæmia.

(*a*) The Plethoric Type. "The patients are mostly middle-aged 'well-to-do' men, in active business pursuits, frequently overworked and overburdened with financial cares;" the healthy, vigorous men who do most of the business in our larger cities and towns. These patients have scanty, high-colored urine, of intensely acid reaction and high specific gravity. On standing a copious deposit of uric acid falls, and there may be slight albuminuria, with small hyaline or "cylindroid" casts. They have coated tongues, constipated bowels, congested livers, pounding hearts, tense arteries, aching heads, and frequent attacks of giddiness, with floating objects or momentary cloudiness before the eyes. They are frequently subjects of apoplexy, which they may survive many years as hemiplegics, with or without grave cerebral failure.

The principle which should guide us in the treatment of this class of lithæmias is very clear, namely, first to reduce the ingestion of

nitrogenous food to the minimum, and secondly to increase the output of nitrogenous end-products to the maximum. But if the *principles* are clear, the reduction of these principles to *practice* is not always easy, for the plethoric lithæmic is generally "a good liver," and he does not take kindly to any material restriction of his diet or drink. Yet this is rather more essential than the administration of drugs, and it is certain that the drugs do little or no good unless the ingesta are properly regulated. But even if the patient is idealy docile, or positively anxious to co-operate with the physician, it is sometimes very difficult to adapt a proper diet to the indulged and pampered palates of the patients under discussion. But my experience has taught me one thing, namely, that an initiatory period of starvation has an excellent effect, both physically and morally. I have many times heard patients express gratification and satisfaction over the departure of their miserable feelings while they were upon an abstemious diet, and they were consequently all the more willing to continue the exercise of a little common-sense in regard to their food.

By "starvation" I mean the absolute abandonment of meats of all kinds, of pastries and sweetmeats, of tea and coffee and of tobacco in all forms, and alcoholic stimulants of every variety, for a period of two to four weeks, or during the initiatory period of medical treatment, to be indicated presently. In lieu of all these, the patient may take milk and cereals, with fruit and Apollinaris or Vichy, or a cup of "postum cereal" in the morning, thin soup with dry toast or soda-wafers and a glass of hot milk at noon, and a small allowance of broiled fish or fowl with bread and fruit at night, or such equivalents of these as the physician may select. But the quantity or "ration" must be limited, so that the digestive tract may have a rest and the scavenger organs may allow themselves a little respite from their habitual overstrain, and at the same time be able to give a little attention to the remedial eliminants which will be administered during this period.

As regards the permanent diet of the plethoric lithæmic, it may be laid down as an axiom that flesh diet must be used sparingly, and that the stronger meats, like steaks, chops, and roasts, must be practically abandoned. But something must be substituted in their stead, and two objects must be kept in mind, namely, to furnish a nutritious and easily digested diet, which shall contain the least amount of nitro-

gen. In daily practice I have found the following diet scheme answer a good purpose: Breakfast—fruit, consisting of oranges, grape fruit, apples (raw or baked), berries in season, melons, plums or cherries, the preference being given to oranges, apples, or grape fruit. The fruit acids certainly promote gastric digestion, and I have long been satisfied that they are decidedly cholagogue, and are therefore eliminants. Following the fruit, cereals of any kind *ad libitum.* We have now a great variety of nutritious and palatable breakfast foods, from which the patient may choose, and he can vary them so as to avoid a wearisome monotony. They should be eaten with a mixture of milk two parts and cream one part, rather than either milk or cream alone. The morning meal may be concluded with an egg on toast, some corn bread, or Graham muffins, or any other equivalent, and a cup of weak coffee or chocolate, or, better yet, a cup of "postum cereal." The mid-day meal is generally the curse of this class of patients. It is usually "taken on the fly" in five or ten minutes, and frequently consists of hearty, solid food, half-masticated, and "bolted" in masses. I have many times watched, with disgusting interest, the "business man's lunches" as they are served here in Chicago and other large cities. It seems incredible that intelligent, educated men—and among them physicians, dentists, and other scientific men—should so far forget the usages of decency as to devour their food after the manner of their canine and porcine ancestors. I am well satisfied that many of my cases of plethoric lithæmia may be traced primarily to the mid-day gorging at the "business lunches" and the subsequent gastro-intestinal turmoil. The medical adviser of such patients should change all this; the mid-day lunch should be a "luncheon," light in quality, moderate in quantity, and nothing more. Milk with bread or rice, or something similar; soup, an oyster stew in its season, or any other light and easily digested food, in moderate quantity and taken in a decent and proper manner, so that it shall not be necessary for the stomach to undertake the added duties of a gizzard. It is especially necessary for the busy, driving men of affairs—those who do the business of the great cities—to persistently and faithfully observe these precepts if they expect to escape the tortures of uric-acid dyspepsia. The evening meal should be "dinner" in theory and fact; to be partaken after the hurry and flurry of the day's work, with plenty of time and the cheerful company of his

family. Soups, vegetables, meat, or fowl or fish in moderation, with special regard for moderation as to roasts and grilles; salads, fruits, and tea or coffee—in fact, a "course" dinner, with due regard to moderation as to number and quality of courses and quantity of food comprising each course. And let this busy, tired, gouty patient be instructed by his physician to leave his business cares and worries down town, so that he can go home to a quiet, restful, cheerful dinner, followed by an evening of relaxation and rest or recreation. Let him be instructed in the lost art of mastication; let him be warned of the danger of rapid eating and of the importance of good, serviceable teeth, free from foul and septic cavities. I have had more than one "gentleman" in my *clientele* who needed jogging on the use of his tooth-brush and a cleansing mouth-wash. If the patient takes stimulants at all, he should be cautious and abstemious—a glass or two of light wine in the evening. If he smokes, let this indulgence be limited to not more than two mild cigars a day, and let the abominable habit of "dry smoking"—*i. e.*, carrying an unlighted cigar in the mouth hour after hour, be forbidden *in toto*.

The medical treatment of plethoric lithæmia is less important than the dietetic, yet it must not be neglected. Cholagogues are indicated in small, frequent doses, and I have been particularly pleased with the mercuric iodides, such as a quarter of a grain of the protiodide, or a thirtieth of a grain of the biniodide three times a day, with a cathartic dose of Hunyadi on rising. This particular class of cases is especially benefited by the rather free use of saline cathartics containing sodic sulphate or magnesium sulphate, with now and then a small dose of mercury, as above indicated.

Among cholagogues, the nitrohydrochloric acid must always take a high rank, and its efficiency is notably increased by combination with a vegetable bitter, like gentian or chamomile. Where there is palpable increase of hepatic volume from hyperæmia or hypertrophy, mercuric bichloride is probably the most efficient remedy, in small but long-continued doses—perhaps a fortieth of a grain four times a day. I have seen several cases of marked hepatic enlargement slowly disappear under the use—or at least *during* the use—of bichloride as above indicated. I think the intelligent and persistent use of these few remedies of much more avail than a greater number which are changed too often to allow anyone to assert its power. In the use

of alterative remedies—I should rather say the *successful* use of alterative remedies—time is the "essence of the contract."

Diuretics or "renal eliminants" are constantly required in the treatment of plethoric lithæmia. Among this class of remedies potassic citrate clearly takes the first place, because it is a pronounced and aggressive eliminant, as the urinometer and ureameter have so often demonstrated. I prefer giving the freshly made salt, which is easily produced by throwing twenty grains of potassic carbonate or bicarbonate into a glass of lemonade, which the patient should swallow during effervescence. This may be given four times a day, *always* when the stomach is at rest, so it shall be absorbed and carried into the blood current as rapidly and with as little change as possible. The salts of lithium and of strontium are of value, and may be used as temporary substitutes for the potassic citrate, but they are less efficient. The acetate and citrate of sodium are also quite efficient, but they also must yield to potassic citrate so far as regards the power of eliminating the nitrogenous waste products through the agency of the kidneys. Other diuretics need hardly be mentioned in this connection, as they are not to be compared with those already named.

These plethoric patients should be sent every few days to take a Turkish or Russian bath (they are about equally barbarous), as they aid elimination by the skin immensely. They should also be made to take the requisite amount of open-air exercise, and nothing is better than vigorous walking, although bicycling or horse-back riding answer equally well.

But all this "availeth naught" unless it is kept up for long intervals; it is of no use to pursue the plan of daily treatment and general regimen indicated by fits and starts only; it must be followed out in all its details as long as necessary, and it must be resumed when necessary, until the absence of symptoms cease to indicate the necessity for its resumption.

(*b*) THE NEUROTIC TYPE. "Very many of the so-called 'nervous temperaments,' 'neurasthenics' and 'nervous cranks,' as well as most of the cases of 'nervous dyspepsia,' are in reality cases of the neurotic type of lithæmia." In other words, quite a large proportion of the cases which are classed as "neuroses" are primarily lithæmics with overstrained nervous systems, which become intolerant of the uric-acid toxæmia. Hence, the "nervous" symptoms, and their name

is legion. Hysteria, melancholia, migraine, epileptiform seizures, cardialgia, and various other "algias," together with a multitude of minor nervous phenomena not worth naming, combine to give the neuro-lithæmic a reputation as unique as it is undesirable. In the treatment of these unfortunate people nothing is more important or useful than rest—rest of mind and body—a prolonged period of absolute separation from business or household or family cares. If the patient is a good sailor, nothing is better than a sea voyage; a quiet sojourn at the sea-shore comes next, with special emphasis on the "quiet." Some cases are greatly benefited by farm life and its freedom from the exactions of society. "Anywhere, anywhere out of the world" of fashion and wearisome parade. Plenty of sleep, plenty of out-door exercise, with some athletics, like rowing, bowling quoits, the health-lift, or whatever the patient fancies in that line.

As to medicine: begin with a few doses of calomel in minute doses several times a day, and a morning aperient of a teaspoonful of Rochelle salt in a glass of lemonade; follow this with a five-grain lithium tablet, four times a day, in a glass of water, when the stomach is off duty, and let this be kept up for several weeks unless it shall be found that potassium or sodium citrate answers better, and this question must be answered by frequent appeals to the ureameter and urinometer. After the torpid scavenger-organs have been aroused and elimination is fairly established a neuro-tonic will be required. The phosphate of iron, quinine, and strychnine ("Aitkin's tonic") does admirably, and may be prescribed in either pill or syrup *immediately* after meals. Most of the preparations of iron are not well borne, but I have had good results follow the use of dialyzed iron, and the old Quevenne's "iron by hydrogen," in rather small but persistent doses directly after eating. But neuro-lithæmics do not bear heroic dosing of any kind. Every now and then the digestive tract will falter, the appetite will fail, flatulence, constipation, nausea, and all the remaining adjuncts of "acute dyspepsia" will suddenly appear. This will necessitate a suspension of constructive tonics, and a return for a few days to the minute doses of calomel with an antiseptic, such as salol. But the tonics should be resumed whenever the digestive tract resumes its work in a normal manner.

Many neuro-lithæmics are much troubled by insomnia. This may sometimes be effectually relieved by massage an hour before retiring.

A dose of bromo-caffeine, or of caffeine hydrochlorate, or of ammonium bromide may be given, or even of codeine if it cannot be avoided. A drive, or a short spin on the bicycle, or even a walk after dinner will promote sleep. A sponging with cold water containing a little alcohol is an excellent hypnotic; and I have even had good success with a "dummy" consisting of a capsule with some indifferent powder, like sugar of milk. But restful sleep must be secured somehow. Alcoholic stimulants cannot be recommended in any form, but a glass of claret at dinner is as harmless as anything, if the patient *must* indulge.

The question of diet can be disposed of in connection with the next group of cases.

(*c*) THE ANÆMIC TYPE. "This type is not quite so common as the other two, but it is by no means rare. The patients are mostly women who have been overworked mentally or physically, or both; frequently young mothers who have borne children rapidly and have been burdened with their care; or saleswomen who are required to stand all day in a constant state of tension and excitement; or ladies who are engaged in clerical work; or school-teachers who find their vocation irksome and exhausting." Of course, males as well as females may belong to this class, but females are clearly in the majority in my practice.

The successful treatment of this type presents some very practical and perplexing difficulties, for it must constantly be borne in mind that we are treating anæmia *plus* lithæmia, or *vice versa.* In the first place, the patient must be allowed a moderately liberal flesh diet; in the second place, elimination *must* be made to keep pace with the demands made upon it. As to diet: milk, of course, but not of necessity, for there are some patients who cannot assimilate milk, and who invariably get gastro-intestinal irritation if they attempt it. There are also many people who *think* they cannot take milk, because it makes them "bilious" or "constipated," as, indeed, it may, especially if it be taken in a faulty and injudicious manner. If a patient with rather feeble digestion will drink rapidly a pint or half-pint of cold milk, without any solid food, it is quite probable that some kind of gastric revolt will follow, and especially if this experiment is repeated again and again. Or, if a patient attempts to drink milk according to some cast-iron rule—so much milk at such a time—gastro-intestinal

revolt will be likely to follow. But if milk is made a part—even the chief part—of breakfast and luncheon, so that it is taken with other food, it is rarely the case that any trouble follows. Hot milk is sometimes borne better than cold milk; a pinch of bicarbonate of soda in a glass of milk frequently prevents eructations; with other people a pinch of common salt will do the same thing. Let the physician study the question himself in its relation to each individual case; then let him engage the intellectual and willing co-operation of the patient, and he will encounter very few failures in his endeavors to substitute a milk for more injurious forms of diet.

Fruits are not objectionable—in fact, they are beneficial in almost all cases. Vegetables, if they agree, may be allowed. Cereals are to be commended with scarcely an exception. Fish, fowl and most kinds of game may be allowed once or twice a day. Sweetmeats and the various culinary frivolities which have little or no nutritive value, but great possibilities as producers of gastric torment, should be debarred entirely. Tea, coffee, and chocolate may be allowed in moderation. Alcoholic beverages had better be let alone.

But what about beef, pork and mutton? They should be allowed once a day in moderation, in spite of the fact that it is a violation of physiological orthodoxy. An anæmic patient must be *nourished;* if he or she happens to be a lithæmic, it is still necessary to insist upon a blood-making diet, but at the same time the lithæmic tendency must be anticipated and guarded against. But it is a waste of time and effort to attempt the restoration and upbuilding of a case of anæmic lithæmia if a diet of red meat is excluded. And just here I wish emphatically to insist that the danger from red meat is not from its use, but from its abuse. A moderate amount—or, more aptly, a *requisite* amount—of red meat is never harmful, even to a plethoric patient; the difficulty is to decide upon what *is* a "requisite" amount, and this cannot be trusted to the judgment of a hearty, hungry, plethoric man who is lithæmic, and, hence, we are compelled to protect him by a process of exclusion. But the case is very different when we are dealing with ill-nourished, neurotic, or anæmic cases of lithæmia; they must be nourished according to their necessities, regardless of the general laws laid down by Alexander Haig, Boix and others, which are entirely correct as abstract scientific propositions, but which do not and cannot apply to all individual cases. It is for the physi-

cian to remember that *he* is treating the particular case in hand, and that Haig and other excellent writers have never seen the patient, and, therefore, cannot be trusted as to details. Time and again I have seen cases of anæmic lithæmia improve upon a diet of red meat after a long and futile trial without red meat, and some of these cases have been markedly arthritic, slightly albuminuric, with pronounced arterial tension. But they had tried milk and cereals and fats and malts and the various artificial "make-ups" which we all know by "samples," their wonderful effects attested by wonderful letters from wonderful doctors; but they did not improve in health and vigor, while the urine remained loaded with uric acid, and the arthritic symptoms lingered. They generally expressed a longing for red meat, or, as one woman expressed it, she "hankered" for a mutton chop. She got it, and, on a moderate or "requisite" mixed diet, including a ration of beef, mutton or pork once a day, she improved slowly but continuously. I have so very many times observed that a restricted, forced, "eat-by-rule" diet is followed by failure of renal function, that I am inclined to formulate an axiom something like this: "An unwelcome diet induces renal inadequacy." Of course, it induces other unfortunate results, but I am dealing particularly with the renal aspect of the subject. These observations on diet and nutrition apply with equal force to many cases of neurotic form of lithæmia.

Little need be said as to the medical treatment of anæmic lithæmia. The general principles of the anti-lithæmia treatment apply. Cholagogues will be needed; gastro-intestinal antiseptics; gentle aperients; alkaline antilithics; vegetable tonics; preparations of iron, manganese, phosphorus and bone-marrow; these are the remedies which will from time to time—and for a long time—be required. But they must all, and invariably, be given in small doses, else they will do more harm than good.

In conclusion, I will venture a few words of counsel, because I hope this paper will fall into the hands of some younger practitioners who are still wrestling with the perplexities of anæmic and neurotic lithæmia.

First. Study each case as an individual entity, not as one of a "group of cases."

Second. Do not expect or promise rapid, perfect, or permanent cures, since it is impossible to change the innate nature of any human being by any mode of "treatment."

Third. Do not cease treatment or allow the patient to pass out of notice when the urgent symptoms have disappeared; a considerable period of mild or alterative treatment will still be necessary to reach the best results.

SOME OBSERVATIONS ON HUMAN TEMPERATURE IN DISEASE.

By NORMAN BRIDGE, M.D.,
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We are always seeking for symptoms that tell the exact nature of the diseases of the human body. If there were idiopathic signs the people would learn many of them, and hardly need doctors, except for the mysteries of treatment; and even these they would more or less master in time, as now they often think they have mastered them. The doctors are alert for the smallest hint of a new sign that can show without error the goings-on in the sick body. The treatment of disease troubles us rather less than the diagnosis; and we are usually more chagrined at our errors of diagnosis than at blunders of treatment.

The temperature of the body in health is maintained at a given point, with slight fluctuations, in all climates and conditions; and it fluctuates peculiarly in disease, and probably with some approach to a typical manner. How these mutations may be discovered and so the clinical thermometer be made more effective in practice has been a long search of the profession.

The temperature of the body in health is kept near a normal line by a regulating mechanism in the nervous system somewhere. More heat is usually made by muscles and glands than is necessary, and the regulation point is chiefly maintained by varying loss of heat, due mostly to the changing size of superficial vessels, produced by the muscular fibres in their walls. These fibres are controlled by nerves, and so by nerve centres.

In fever there is a regulation point as truly as in health, only it is higher and less constant. With its rise and fall there are frequently attendant symptoms that are curious and paradoxical, although probably conservative, as the subjective sensation of cold with a rising

temperature and of heat with a falling one. It is not true that more heat is generally produced in the body in fever than in health under full exercise, but the contrary. It is only the regulation point that rises always.

What makes the regulation point rise? Why do the nerve centres controlling the heat manufacture and dissipation change their force and action under certain influences which we call causes of disease? These questions go at once to the core of the clinical phase of the subject.

Doubtless several pathological conditions produce the rise of the regulation point, and the accidents to these factors may cause all of the fluctuations. There is no great change in the regulation point below the normal; whenever, therefore, we speak of a change we mean a change above the physiological par, and that is fever. Yet there are disorders, of a chronic sort mostly, where the temperature is for weeks or months slightly below normal at certain or all times of the day. Myxœdema is one of them.

The tendency of professional thought is now toward attributing all fever to certain substances in the blood produced by microbes or to the microbes themselves. The proof of such toxic influences is overwhelming, but they are not the sole causative forces. And if we shall ever be able to catalogue all the causes we shall need to discover the one essential factor in the complete solution of the question—namely, the manner in which the nervous regulating machinery is ultimately affected by toxins or what not.

In studying the fluctuations of temperature we may profitably set a few things we know over against some that we do not know, and so hope to gain some practical lessons for the more efficient care of the sick.

1. We know that pus poison—that is, the micro-organisms of pus and their products absorbed into the general circulation—causes fever. We probably often encounter fevers that we fail to understand, which are due to small accumulations of pus hidden away somewhere in the body; but that is no justification for the assumption that in every inexplicable prolonged fever such a source of poison must exist.

2. Dead tissue, as the products of changes in greatly overworked muscles, albuminous bodies set free from these tissues and floating in the blood, probably cause fever.

3. Slight elevation of temperature is produced by absorption of albuminous toxic substances from cyst cavities in various portions of the body, as the skin, the scalp, and the ovaries, that leak into the connective tissue about them and undergo absorption. These are not the products of pus poison.

4. Then we know that certain poisons, almost positively microbic, are taken into the body from the air, or in food and drink, and produce fevers (with possible eruptions upon the skin) which run a distinct course and terminate spontaneously if the patient lives. The fever begins after a period more or less definite (an average of perhaps a week) of so-called incubation, and often begins suddenly. Probably a certain amount of the poison must be introduced to cause fever, or some especial susceptibility must exist to make possible the cycle of events referred to. The theory seems plausible that the self-limitation of these diseases is due to the rapid accumulation in the body of the products of the microbes, first depressing, then destroying them; or that the microbes, by some reaction of the physiological forces of the system, provoke the formation of a toxin capable of destroying them in a few days.

This class of diseases includes, of course, typhoid, typhus, scarlet, and yellow fevers, measles, German measles, whooping-cough, varicella, variola and its modifications, pneumonia, plague, diphtheria, erysipelas, follicular tonsillitis, possibly acute rheumatism, and unnumbered other and yet unknown diseases. The list is not complete, nor will it be probably for many decades to come. We shall go on, as we have done, discovering new diseases out of the symptoms that have been the common but misinterpreted observation of centuries.

5. We know that high temperature results from certain conditions of malarial organisms in the blood, the forms of fever differing with the life-history of the plasmodia. Here, too, personal susceptibility plays some part in the process; all people do not resist or succumb alike, nor do all who are affected suffer alike, either in manner or degree.

6. High temperature of the environing atmosphere, with or without the sun's rays, under certain conditions cause alarming pyrexia known as thermic fever or sunstroke. It is probably due to inhibition or stimulation of some of the heat centres or other part of the heat-regulating machinery. But microbes have even been accused of inducing

these cases, and it is not very unlikely that toxins are produced in the tissues by the heat and disturb the regulating centres, and so cause fever as the toxins of bacteria do.

7. We know that inflamed follicles of the tonsils may cause sudden high temperature, lasting a few days and subsiding spontaneously, while the same sorts of microbes are found within them that are discovered in normal follicles. How far this fever should be attributed to pus poison is unsettled.

8. Inflammations in general are attended with fever. Formerly we thought they always produced the fever; but now we know the two events are frequently co-results of some other causative influence.

Where some irritant, applied locally, depreciates the vitality of a part, and inflammation results, and then fever, it is rational to assume that the microbes of pus may find there a culture medium, and infect the system as they do from an abscess. But when, as in the pneumococcus infection, we know a fever *precedes* the inflammation in the lung, it is clear that the microbic poison in the blood does the whole mischief. And nobody knows how much of some toxin may find its way into the circulation as the result of an inflammation and help to cause fever.

9. We know, but usually forget, that the commonest serious diseases of the kidneys are free from fever as well as from backache; that practically no disease of these organs causes fever save the rarest and somewhat questionable acute parenchymatous inflammation of the renal or the perirenal tissues, and that in general only those with calculi cause pain in the back. Bright's disease fails to do either in any of its multifarious forms.

10. We do not know how much fever is caused by tuberculosis apart from that due to pus microbes encouraged to grow by the tissue necrosis, which is nearly always induced by this remarkable disease, and to absorption of products of the necrosed tissue itself. Pure tuberculosis may, but usually does not, cause fever under circumstances that permit us positively to exclude the presence of pus products or those of inflammation or necrosis, whatever they are, except where the tissues of or about the central nervous system are directly involved.

11. We do not know why fever rises or falls rapidly or slowly. There are ingenious theories about it, but no proof.

12. We lack positive information to explain the genesis of many cases of fever which occur suddenly in children (and occasionally in adults) and are connected in some way with gastro-intestinal derangement. The difficulty is that at times apparently exactly similar disturbances are unattended by fever. An easy claim is that ptomaïnes from decomposition of intestinal contents cause them. It may be that a part of the cases are so caused, but as to many of them it is unproven and appears unlikely. The symptoms of constipation and diarrhœa, of pain and swelling, are, so far as any clinician can tell, exactly the same a hundred times (and even many times in the same patient) when no fever occurs. It is easy to say that the fever must be due to some peculiar chemical or vital change not present in the other cases; and it is true that if abnormal metabolism within the digestive organs or elsewhere can cast into the circulation such substances as pepsin, peptones, albumose, fibrin ferment, or diastase, fever is produced. That such events do occur in these cases is largely conjectural.

13. We may fairly be in doubt to what degree nervous perturbation alone can cause fever. In a pus-poisoned patient, or one with an essential fever or tuberculosis, where there is even a trifling elevation of temperature, this is often made worse by mental excitement or by work. Can the excitement alone produce it when no poisoning exists? Probably not, since the greatest mental excitement (grief, fear, joy, and anger) in a well person usually causes nothing of the sort. And in the cases where the fever is produced or raised by activity, is this due to the nervous excitement or to physical labor? A patient with tuberculosis or pus absorption, who keeps perfectly quiet in body and mind, may have a maximum temperature of perhaps 100° F. some time in the day; but a walk round the block or a business discussion of half an hour will carry it to 101° or 102°. This is so well known that in sanatoria for consumption the rule is general that only patients wholly free from fever are permitted to exercise.

It seems impossible to deny that psychoneuroses may disturb the heat-regulating machinery and produce positive fever. But the apparently fabulous fever reported of certain cases of hysteria is subject to honest doubt. Many physicians even deny that pure hysteria can cause fever. But the pronounced paralysis of motion and sensation, the spasms of several kinds, the hyperæsthesias, and the erratic aber-

ration of functions of almost every sort and degree, known the world over as the result of hysteria, ought to make it easy to believe that the heat centres may be involved as well. And if hysteria can affect them, then there is no limit to their possible degree of aberration, except the capacity of the tissues to produce and husband heat, and their tolerance of high temperature without coagulation.

14. There are numerous slight attacks of fever that seem inexplicable. They last short, and have few or no focal symptoms or signs, and no evidence of microbic poisoning save in the mere phenomenon of fever. That this fact is some evidence cannot be denied. But if the reasoning is sound, then it is fair to assume that hitherto unknown microbes (or their life-history) capable of producing definite febrile action are yet to be discovered. Time was when rōtheln was some erratic form of measles; now we know it to be a specific and probably microbic disease, differing wholly from the latter, and protecting its victim as measles does. Time was when myxœdema was a freaky form of dropsy; now we have its perfect explanation—with what glory to modern pathology everyone knows; and cretinism is analogous to it. Why should we not expect to find that other specific diseases have been occurring under our eyes and observation for years without our knowing it? And why should we, every time we are confronted with one of these inexplicable fevers, attempt to make it fit some of the grooves of known febrile disorders, as typhoid or malaria, or be unhappy if we cannot? The effort to do this leads us often to hazard a diagnosis that, being false, we are forced to change in a few hours, or that we foolishly feel compelled to stick to throughout the case, to our discomfort and loss of self-respect. And we gain little, save with a peculiar portion of the public, when we load our uncertainties off upon some convenient scapegoat, the existence of which can neither be proven nor disproven. Formerly the scapegoat was malaria; now that malaria is so perfectly demonstrable, it is oftener grip—that cannot be well demonstrated; for the necessities of a scapegoat require that it shall be airy, indefinite, and incapable of proof.

During this very season numerous cases have occurred in many states of suddenly oncoming fever, lasting two or three days, with slightly swollen, red pharynx, and no apparent follicular inflammation. The general malaise, weakness, and perhaps headache of the

fever state have come and vanished in this brief period. Perhaps these cases were the true influenza; perhaps some other zymotic disease as yet unidentified.

The clinical significance of fever depends on other circumstances than the fever itself. High temperature, *per se*, is of small account. With a spot of sharp abdominal tenderness or rigidity of muscles, or with unconsciousness or spasm, coming on with fever, it may mean very much, as may a long-continued slight elevation of temperature without focal symptoms. This last leads us, especially in chronic cases, with slight indisposition, to hunt long and faithfully for the cause. Clinically it is a valuable pointer.

The temptation among practitioners to treat the fever state is almost irresistible, but it should not ordinarily be treated. The wholesale medication so often done for this purpose is mischievous in the extreme.

If unconsciousness or convulsions attend high fever, showing brain involvement and perhaps a paralysis of some of the heat regulators, the temperature should be promptly reduced by baths, for through this act directly, or by some increased elimination it produces, the convulsions usually cease and consciousness returns. It is not true that fever of moderate degree must be brought down at once; fever often endures for long with little harm, as is shown in many cases of tuberculosis of the lungs, where a slight daily elevation of temperature may persist for months with little impairment of the strength or general physical condition. Slight fevers may occur daily with no cachexia for a long time; the system becomes adjusted to it and the secreting organs are little disturbed.

A very high fever, or one that produces marked head discomfort, or great restlessness, may not improperly be reduced by means of coal-tar preparations or the application of water. But it is not proven that in typhoid or other fevers the antipyretic drugs for any ordinary febrile temperature have shortened the attacks or increased the percentage of recoveries, and the habit of using them for this purpose has undoubtedly done much harm and very little good.

Probably the drug most extensively used for lowering fevers during the last thirty years (notwithstanding the free prescribing of the coal-tar preparations) is aconite; yet to this hour I am ignorant of any proof whatever that this drug can lower the temperature of fever,

except by injuriously lowering the vitality of the patient. It may slow the heart and lessen nervous perturbation; but that is quite another thing.

We often find ourselves considering in the most serious manner as a grave thing the direct effect of a temperature of say 102° F., and lasting for a few hours or for a day. And we have connived at the belief by the lay people that such a fever is dangerous. If placebos are needful for the *morale* of the patient, there is no objection to giving some innocuous thing ostensibly for the fever, but for doctors to regard it as necessary on other grounds is unscientific and poor practice.

A free catharsis at the beginning of sudden fever often gives a sense of relief, probably by removing ptomaïnes and other effete matter from the intestines, and in this or some other way removing congestion (or a sense of it) from the head. But except by removing ptomaïnes there is small proof that it lowers the temperature; and evidence of this latter even is not of the best.

It is, of course, always in order to attempt to remove or destroy the causes of fever. Some of the more tangible ones, especially those of a surgical character, we may deal with effectively. We may evacuate effete matter from the alimentary canal and increase the toxicity of the urine, which it seems clear is one of the eliminative effects of the Brand treatment of typhoid. But it is doubtful that diuretics produce this effect very much, although many forms of treatment may help the system to free itself from the toxic influence.

The service of this sort which we can render is very sharply limited, and may be roughly indicated as follows:

1. Pus pockets, suppurating surfaces, and cysts leaking into the connective tissue, and so reaching the general circulation, may sometimes be evacuated or removed.

2. Inflammation may be assuaged, cured, or waited for.

3. Ptomaïnes in the alimentary canal may be evacuated by a cathartic if they do not directly bring on a remedial diarrhœa.

4. Malarial plasmodia may be effectively dealt with; and we have, fortunately, one drug proven to have a positive action against these parasites.

5. The causes of the essential fevers, that obviously consist of specific microbes which run their course in definite periods, are usually

destroyed by the conservative havoc wrought by the products of the microbes themselves. No drug is capable of destroying them, and, on the basis of present knowledge, it is idle to medicate by such means. But we are beginning to know that the destruction of these poisons is possible by artificial means acting like the physiological forces. The success already attained in a few diseases, most notably diphtheria, is crucial proof of the possibilities in this direction, and is reason for the faith that we shall soon be able to deal with many diseases in the same way. This is the direction the efforts of every clinician ought to take, and we await the beck of the votaries of bacteriology and pathology.

It is hard to keep the practising part of the medical profession plumb, as it is the lay world. We easily drop into habits of prescribing for insignificant things, to the neglect of the few indications that make for the patient's better comfort and greater prospect of recovery—the two objects that alone justify the existence of doctors. We give aconite or other drugs for slight fever and to bring down the pulse; digitalis, because the pulse is weak at the wrist (even when the weakness is apparent and not real, but due to the muscular and nerve fibres of the vessel walls; we give calomel to clean off the tongue; prescribe for dry and rough skin and for cold, clammy skin; and for temporary dark coloration of the urine—and all as though such things were consequential and not the necessary, harmless accompaniments of many sicknesses of all shades of severity. Worse, we often prescribe thus to the injury rather than the benefit of the patient, and by pursuing such methods hide from our own eyes the manner of reasoning that means growth and the measures that, besides being scientific, are genuinely useful for the health and longevity of the sick.

SARCOMA OF THE STOMACH.

By GEORGE DOCK, M.D.,
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T. J. W., married, merchant, fifty-five years old, was admitted to the University Hospital, January 18, 1900, on account of loss of strength and weight, and distention, burning pain, and tumor in the stomach region. The family history is negative. In early life the patient had whooping-cough and measles. While in the army during the Civil War he had several attacks of intermittent fever, and was jaundiced four months. Ever since then he has been constipated. Up to two years ago he had every summer an attack of pain in the abdomen, with vomiting, fever, pain in the head and back, ending with diarrhœa. Has never had jaundice after these attacks. During the last four years was postmaster; had long hours, ate hurriedly and heartily, almost without mastication. Thinks this has aggravated his present disease. Uses tea and coffee in moderation; smokes, but does not use alcoholics.

The present disease began in December, 1897. Constipation was very troublesome and the patient lost weight. Soon after this he noticed a heavy sensation in the stomach region. In the spring of 1898 had an attack of pain in the right hypochondrium, moving down toward the hip, cutting, of short duration, but followed by pain and tenderness in the liver region, in the back, and the right side of the abdomen. Never had nausea in the attacks; pain made him double up. Had a number of very severe attacks of this kind. Gallstones were suspected, but never found in the stools. In April, 1898, began to vomit. At first vomited only what had been last eaten; later, articles eaten a day or so before. Never vomited blood or dark material had regurgitation of irritating fluid.

In July, 1898, a tumor was discovered just below the ribs in the right nipple line. This he thinks grew smaller. During all this year the abdomen was distended more or less. In December, 1898, at the advice of a friend, began to use the stomach-tube, washing out the stomach three times a week before breakfast. This gave much relief, but was associated with great loss of weight. By the end of three weeks he had lost twenty-five to thirty pounds from his normal weight, had no appetite, and could take nothing but milk. He was then treated by a physician, who stopped the lavage, gave strychnine, laxatives, etc., and looked after the diet. He then improved, gaining thirty-five pounds in four months. The pain almost disappeared. In October, 1899, he began to vomit after almost every meal, lost weight and

strength; the appetite failed; the stomach became greatly distended; sour, burning fluid was regurgitated. Food remains of the day before were found in the vomitus, but there was never any blood. Thinks the tumor is no larger than when first noticed.

Status præsens, January 18, 1900. The patient is five feet six inches in height; weighs now 110 pounds; frame is of medium size, panniculus absent, muscles small and flabby; skin is loose, inelastic, rough, dry, sallow; there is marked nodular myoidema; mind clear, expression languid; marked arcus senilis. The visible mucous membranes are pale; there is no œdema; no enlarged glands; joints normal. The tongue is not large, the papillæ not enlarged; surface moist; thin white coat. Teeth are defective; upper plate. The thorax is of medium size and well formed. Auscultation and percussion of lungs and heart negative. Radial arteries tortuous, walls uneven; pulse, 64, regular; tension moderate.

Abdomen in general is below the level of the ribs; but above the umbilicus tumors of considerable size form and disappear, move from right to left, back to right and downward; they can easily be brought out by tapping on the abdomen. Auscultatory percussion shows change of note an inch below the navel. There is succussion to the line of the umbilicus. Just below the edge of the ribs between the right nipple and parasternal lines is a mass about the size of a hen's egg, hard, smooth; it moves down with inspiration and is retracted with considerable force in expiration. Liver-dulness extends from the sixth interspace to the edge of the ribs; the organ cannot be felt. The splenic dulness is small; the spleen cannot be felt. The right kidney can be felt on deep breathing.

The blood flows freely and is of good color. Red corpuscles, 4,960,000; leucocytes, 7250; Fleischl, 75; specific gravity, 1056. Differential count of leucocytes shows lymphocytes, 7; polymorphonuclear, 89; transition, 2; degenerates, 2 per cent.

10 P.M. Stomach prepared for Boas gruel. 700 c.cm. of fluid aspirated; first part light, then darker, with acid odor, much foam, and gas-bubbles breaking after standing. Lower layer of white granular material, with undigested meat, potatoes, milk. Middle layer of clear, pale-yellow fluid; top layer of foamy mucus with sarcines and yeasts, fat, muscle fibres, and starch. No blood, no pus, nor tissue.

19*th*. Boas breakfast aspirated after forty-five minutes. 200 c.cm., pale-yellow, cloudy fluid; odor of apples. Reaction acid to litmus; Congo dark-blue; Günzberg negative, dimethyl positive; Uffelmann negative. Total acidity, 51 = 0.18615; combined acid, 7 = 0.02565; free HCl, 28.5 = 0.10402; organic acid and acid salts, 15.5 = 0.05657. Digestion in test-tube very slow, even with addition of HCl. Sediment: food remains, few leucocytes, some very small bacilli—not Oppler-Boas.

Stomach distended with CO_2. Lesser curvature just above the umbilicus; greater curvature four inches below. Stomach is perpendicular; tumor is behind the right end of the distended stomach.

Urine examination: Excess of indican, otherwise negative. Examination of stool negative. Patient was given special diet for dilatation.

20th. Prepared for Boas gruel at 11 P.M. The washings contain sarcines and small bacilli as before.

21st. Boas meal, one-half hour. 400 c.cm. dark yellowish-brown fluid, containing food particles and sarcines. Günzberg positive; the quantitative tests about as before; digestion in test-tube slower than before. Lavage was repeated every two or three days, according to the indications. There was always more or less fermentation, with sarcines. Hydrochloric acid was always present; lactic, never. The patient gained three pounds in ten days. The tumors ceased forming in peristalsis.

The diagnosis was dilatation from tumor at the pylorus, probably the scar of an old ulcer. When admitted the patient laid much stress on the history of paroxysmal pain, with soreness in the epigastrium, vomiting, etc. Although there was no history of hemorrhage, yet the symptoms in the early stages had not been carefully observed. There was evidently an adhesion between the liver and the stomach tumor, and, on account of the history, long duration, and absence of more positive evidences of malignancy, I thought this pointed rather to hypertrophic scar than to new-growth. Largely on the ground of probability, the likelihood of carcinoma being present in the tumor was represented to the patient. Other possibilities, especially sarcoma, were considered, but the features of the case were not considered to admit a differential diagnosis.

The patient was advised to submit to an operation, with a view to carrying out the best treatment permitted by the local conditions when examined directly. He consented, and pylorectomy was made by my colleague, Dr. C. B. Nancrede, Professor of Surgery in the University of Michigan. The operation, having been unavoidably postponed, was done February 5, 1900. The part removed represented about one-third of the long axis of the stomach and about two centimetres of the duodenum. The tissue removed seemed to be well clear of new-growth at its extremities. No metastasis could be found. Uninterrupted recovery followed the operation. The patient sat up in three weeks and was discharged in five weeks, having gained the weight lost after the operation, and is still increasing rapidly.[1]

The piece of tissue removed measured 6 cm. along the lesser curvature. The pylorus was almost closed. Projecting into the lumen was a tumor of oval shape about 6 by 4.5 cm. in diameter, occupying the posterior wall of the stomach. The serosa behind the mass was covered by stringy adhesions, which had been separated at the operation. The tumor was smooth, elastic, and on section showed a grayish-white, almost homogeneous surface, yielding few cells on scraping. Near the main mass were several smaller nodules having similar microscopic characters. The mucosa in the uninvolved part

[1] A letter of May 14th states that the patient gained thirty pounds in the two months after his discharge, weighing as much as he ever did; could eat anything, and was free from symptoms. It is, of course, too early to speak of radical cure.—G. D.

of the stomach was thick and uneven. Over the tumors it was smooth, in places red, but nowhere eroded or ulcerated. Section showed the new-growths to be chiefly in the submucosa and muscularis. Microscopically the tumor is a lymphosarcoma, with a well-developed reticulum containing small cells in its meshes.

The new-growth invades the muscularis, but does not show a tendency to affect the mucosa The mucosa in parts distant from the tumor shows interstitial infiltration without evidences of sarcomatous formation.

Sarcoma of the stomach is not often reported. Schlesinger,[1] who made a careful study of the subject in 1897, was able to find references to only 33 cases, and added 3 of his own. I have found records of 10 other cases in periodic literature, 3 of which (5, 10, and 13) I have not been able to obtain, besides a few cases briefly mentioned in text-books. I refer to 3 of the latter. One of the cases cited by Schlesinger (Hardy) seems to have been one of cancer, as Tilger has suggested. On the other hand, it is probable, as Brooks says, that cases of sarcoma of the stomach have been incorrectly reported under the name of cancer.

The absolute rarity of the affection is beyond question, and the only reason for calling attention to it again is to ascertain whether recent additions make it necessary to revise the older views. This is all the more needful because the present case differs in certain respects —notably in the results of the analysis of the stomach contents— from those previously reported.

In the following it is unavoidable that I follow Schlesinger closely, since my examination of the literature largely confirms his conclusions. I cheerfully acknowledge my obligation to his excellent article, and refer to it for the earlier literature.

Sarcoma of the stomach may be primary or secondary, and the latter is perhaps more frequent than secondary cancer, but is rarely of clinical interest.

Sarcomata of several varieties have been found as primary growths in the stomach—*i. e.*, spindle-celled, fibrosarcoma, myosarcoma, myxosarcoma, angiosarcoma, and round-celled sarcoma. The majority of the latter were probably lymphosarcomata.

The primary growth may originate in any part of the stomach. Schlesinger found the greater curvature often involved, especially by the varieties that form tumor masses rather than flat infiltrations. In several recent cases the round-celled or lymphosarcomata developed

in the pyloric region, and some of the others in the posterior wall. The reported cases are too few to establish rules regarding location, such as are admitted in the case of cancer.

As regards size the tumors vary greatly, but a rather large proportion reached a size unusual for gastric tumors. In Brodowski's case, and also in Cantwell's,[11] the tumor weighed twelve pounds. In Baldy's[8] case the mass filled the abdomen from the ensiform to the pubes. The growth begins in most cases in the submucosa, or, less frequently, the muscularis.

Primary lymphosarcoma of the stomach sometimes produces extensive flat infiltrations or local thickenings, or, as in the present case, circumscribed tumors. The mucosa is rarely involved early, but may be stretched or its nutrition injured by pressure, and it may then ulcerate. In some cases the tumor projects outward. Softening is not unusual, especially in the larger tumors. Suppuration may also occur, and in either case peritonitis from rupture may follow. In some cases rupture has occurred into the cavity of the stomach.

Metastases occur, as in other sarcomata, and may be found in the neck, pharynx, or various parts of the abdomen. In some cases, even with primary lymphosarcoma, the disease has lasted a long time without metastases.

As regards age, Schlesinger found lymphosarcoma of the stomach most frequent between twenty and thirty-five; other varieties somewhat later. In Finlayson's[10] case a rickety and feeble child was affected at three years, and died six months later. In Westphalen's[2] case of myxosarcoma the patient was twenty-eight. Men are more frequently affected than women.

The study of sarcoma of the stomach throws no light as yet on the cause. In Brooks'[9] case the disease began, apparently, in the scar of a bullet wound acquired many years before.

Our knowledge of the clinical features is even more meagre than that of the anatomical facts, since only a small proportion of cases were carefully examined during life.

The mode of onset varies, but is often insidious. Thus, in Baldy's[8] remarkable case the stomach had "never given the patient a day's trouble;" the appetite was voracious; there was no vomiting. In Cantwell's case also there were no gastric symptoms. In both these cases the disease began in the posterior wall. Later, such symptoms

as loss of appetite, vomiting, and pain of various kinds and various degrees of intensity occur. The pain may be referred to the epigastrium or the back. Hemorrhage is almost never an early symptom, but when it occurs may have the different characteristics that present themselves in cancer, the blood resembling coffee-grounds, or being fresh or clotted. In Hartley's[4] case there was a history of coffee-ground vomiting five years before, after long-standing dyspeptic symptoms. A year before the operation, at which the mucosa was found not ulcerated, there was vomiting of coffee-ground material and also clots. Blood, more or less altered, may also appear in the stools.

If there is tumor, it presents the same variety of physical conditions as in cancer, except in cases with colossal growth, when the relations may be impossible to make out clinically and difficult to understand at an exploratory operation. If in the pyloric region obstruction, dilatation, increased peristalsis, stagnation, and decomposition, lessened diuresis, concentration of the blood, even tetany, may result. Dilatation may occur without obstruction in the case of wide-spread infiltration.

Examinations of the stomach contents have been made in only a few cases. In all but the present one (nine others reported) free HCl was absent; in most of them lactic acid was present. In one of Schlesinger's cases there was free HCl in the beginning, but it disappeared. Sarcines were absent from the other cases as a rule, and in one of Schlesinger's cases long bacilli were present. In some cases there was no blood in the stomach contents, but in others there was, so that the resemblance to the findings in cancer is very close. So far as the present case is concerned, the presence of free hydrochloric acid and sarcines does not materially weaken the conclusion that the stomach contents in both cancer and sarcoma have the same characteristics, since it has long been known that absence of hydrochloric acid and presence of lactic acid are not due to the cancer as such. In fact, the conditions observed in my case are found in some cases of cancer of the pylorus up to a late period.

The blood in the cases of sarcoma of the stomach hitherto examined showed diminished red cells and hæmoglobin and usually leucocytosis. No examinations seem to have been made regarding digestion leucocytosis.

The average duration of the disease is one to one and one-half years.

The diagnosis of sarcoma of the stomach has rarely been made during life. In the case of Westphalen it was based on the microscopic examination of a bit of tissue. In one of Schlesinger's cases the diagnosis of lymphosarcoma was made, based on supposed metastatic growths in the intestine and lymphatic glands and enlarged spleen. Autopsy revealed myosarcoma with suppuration and perforation of the stomach. There were a few retroperitoneal metastases. Riegel[14] mentions a case in which a large sarcoma nodule was vomited and the diagnosis made. There were in the same case metastases in the skin. The danger of depending on coexisting tumors in the skin is made clear by von Leube,[15] who found in one case sarcoma in the skin and an epithelial tumor in the stomach.

This symptom is probably as little reliable as two others mentioned by Schlesinger: enlargement of the spleen and swelling of the follicles of the tongue—both thought by Kundrat to be common in lymphosarcoma. They may sometimes enable one to correctly recognize gastric sarcoma in a late stage.

So far as the earlier stages are concerned we have no specific symptoms of sarcoma of the stomach, and even when tumor is present it cannot be positively differentiated from cancer. Just as in cancer, it is important to discover the affection of the wall early, and, if possible, to carry out either radical or palliative operative treatment without taking time to make a histological diagnosis from the clinical features. If discovered too late for this, the treatment must follow the same general lines as for other tumors of the stomach. The results of operations compare favorably with those for other malignant stomach diseases. In Cantwell's case a spindle-celled sarcoma involving five inches square of the stomach wall was removed. The patient was free from symptoms for six months after the operation, and then a secondary tumor was discovered.

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PERICHONDRITIS OF THE LARYNX IN TYPHOID FEVER.

By M. HOWARD FUSSELL, M.D.,
OF PHILADELPHIA.

THE chapter in Professor Keen's admirable work on *Surgical Complications and Sequels of Typhoid Fever* leaves little to be said upon the interesting subject of typhoid affections of the larynx, and this paper will simply add a new case to the already growing list of recoveries from this former almost uniformly fatal complication, and compare the new case I have to record with a fatal case I reported before the American Medical Association in July, 1897, and which Keen has figured in his book. The statistics I owe largely to Keen's book.

The subject of perichondritis of the larynx in typhoid fever is but lightly touched upon in the text-books of medicine, which makes an excuse for this paper rather than the simple report of a case. Few of the text-books mentioned the complication, though Osler and Strümpell speak of it.

A catarrhal laryngitis, and in some cases superficial ulcerations of the laryngeal surfaces, occur without giving rise to symptoms which alarm either the patient or the physician. This was the fact in both my cases, and is so graphically described by Lunig[1] in his article upon this subject, that I feel that I can do no better than follow Keen and quote what he says *in toto:*

> The fact that the patient at the time when the lesions in the larynx are so wide-spread that they ought to be recognized clinically, lies in typhoid apathy, and often makes no complaint of his suffering, is a great hinderance to the clinician. All the more is it his duty not to allow even slight complaints, especially if they arouse even a suspicion of any laryngeal complication, to pass unnoticed. . . .

[1] Archiv für klin. Chirurgie, 1884, Band xxx. p. 225.

In the histories will be found the oft-recurring remarks, "The patient was doing well," or "he was slightly hoarse," "complained slightly of dyspnœa," etc. . . Physician and patient together rejoice over the daily progress toward convalescence; of the still slight but persistent trouble in the throat scarcely a word is said, until all at once—an exposure to cold, a little walk, are then usually blamed for it—the hoarseness increases, and swallowing becomes markedly painful. The picture now quickly alters. Soon, often within a few hours, come dyspnœa and suffocative attacks. Sometimes, even during the very first day, the anxious scene of laryngeal stenosis sets in, with stridor, inspiratory depression of the neck and chest-wall—the unrest of despair, a struggle with death. The face becomes livid, the respiration becomes rapid, wearisome; the auxiliary muscles of respiration are all called into play; sometimes the respirations are prolonged and noisy. The patient can find no rest; the dyspnœa even prevents the taking of nourishment the expectoration of the increasing mucus becomes imperfect; soon attacks of suffocation recur. Either a tracheotomy must now be done immediately or the patient, if he is weak, may choke to death, even in the first attack. More commonly, however, the attack subsides, and a slight improvement with a short sleep will ensue. Expectoration of bloody mucus, masses of pus, and, in some cases, even of pieces of cartilage diminish the symptoms, and show at the same time that the real cause of the dyspnœa is not a catarrhal œdema or dropsical swelling, but a destructive ulceration even of the cartilages. Often, also, there is severe fever. Thus pass on, it may be even days and weeks, easy breathing alternating with the suffocating attacks. The alternative is only a finally fatal attack of suffocation or a late palliative tracheotomy with all its uncertainty. . . .

In these cases the objective signs of laryngeal stenosis, on which we generally depend, are much less marked; stridor, movements of the pharynx, inspiratory depression, action of the auxiliary inspiratory muscles—in short, everything upon which in the healthy we made the diagnosis of narrowing of the air-passages is, in the vita minima of the weakened patient, far less outspoken, and easily deceives us as to the degree of the danger of suffocation. The striking suffocative attacks, with arrest of respiration, so alarming even to the lay observer, are less noticeable, since the struggle of the patient with the mechanical obstruction quickly fails or is quickly abandoned. The condition passes into a death agony, with œdema of the lungs, without the stenosis seeming to have reached a threatening degree. . . . And thus one sees, often with astonishment, in the reports of the necropsies, how often the stenosis and destruction of the cartilages occurs, as it were, "without even any symptoms."

This description details in most graphic words the condition in both of my patients. In the first, nothing was noticed until severe symptoms came on. In the second, stridor was the first noticeable symptom.

Frequency of Occurrence. The infrequency of this complication may be judged from the fact that in a series of 2000 autopsies for typhoid fever reported in the *Münchener medicinische Wochenschrift* for 1891 there were 15 cases of perichondritis of the larynx, or seven-tenths of 1 per cent. of the cases.

Keen has collected 221 cases:

Age of 146 cases: Under fifteen years, 12 cases; fifteen to twenty-five years, 87 cases; over twenty-five years, 47 cases.

One of my cases will be found in the second division of this list, the other in the last, their ages being respectively eighteen and thirty years.

Sex of 148 cases: Males, 119; females, 29. Both of my cases were males.

Site of Stenosis. Supraglottic, 50; infraglottic, 56; in the glottis, 18. In one of my cases the cricoid was affected and the stenosis was below the glottis. In the other the intra-arytenoid space was the beginning seat.

Date of Onset. This is generally late in the course of the disease; in my first case convalescence was well established. On the sixth day, after the temperature became normal and after a mild attack of fever, stenosis suddenly developed. In my last case the first symptoms of stenosis occurred on the forty-fourth day of the disease, fourteen days after the beginning of normal temperature. The patient up to this date, however, was extremely weak.

Mortality. Where there is an actual necrosis of the cartilage the mortality is exceedingly high; of 75 cases reported by Keen 71 died, or a mortality of 95 per cent. One of these cases (my own) gave excellent opportunity for operation, but the chance was refused by the stupidity of the relatives. In all the forms of stenosis, of 197 cases 132 died and 65 recovered, a mortality of 67 per cent. Of 98 cases not operated upon 21 recovered and 77 died, or a mortality of 78.6 per cent. Of 99 cases operated upon 44 recovered and 55 died, a mortality of 55.5 per cent.

This mortality of operated cases is doubtless higher than it will be in the next equal number of cases operated upon, because operation will not be delayed, and consequently more lives will be saved. The danger of delay is well illustrated in my two cases. In the first evident stenosis was present for at least forty-eight hours before

death occurred, and in this case the stenosis was unquestionably due to the protrusion of the abscess wall into the lumen of the larynx, as there was very little œdema.

In the second case the gravity of the situation was recognized quite early enough; but the boy almost lost his life, owing, first, to procrastination, and, when operation was decided upon, to the delay of a train bearing the surgeon.

Laryngeal examinations were made in thirty-two instances. In all cases there were redness, swelling, and œdema of the portions of the larynx. In my first case the laryngeal examinations revealed externally much tumefaction and tenderness over the entire larynx. Internally there was simply a red, swollen mass seen below the cords; the cords themselves were red and swollen.

In my second case, underlying the epiglottis was a huge red œdematous mass, entirely obscuring the cords, this occurring at least twenty-four hours before symptoms of severe stenosis appeared.

Final Results of Cases Operated Upon. Lunig has collected 60 cases which recovered after tracheotomy; 11 were able to dispense with the use of the canula in periods varying from seven months to six years, but the other 49 were forced to wear the tubes during the remainder of their lives. Some could go without the tube in the daytime and were forced to use it at night. The latter was the fact with my second case; he did not finally dispense with the tube for six months. Soon after he was about, however—indeed, in four or five weeks—the tube could be occluded for hours at a time; at night, however, he was forced to open the tube.

The following cases came under my observation:

CASE I. (reported before the American Medical Association, 1897).—I respectfully refer to that article, but quote an abstract. The patient suffered from an attack of typhoid fever, as proven by the symptoms and the post-mortem.

On the fifth day of convalescence, without previous laryngeal symptoms, he swallowed a hard piece of apple, and suddenly began to suffer from symptoms of laryngeal stenosis.

Three days passed before the death of the patient, in which he suffered tortures, but operation was refused by the family, and this was acquiesced in by the physician in charge.

The post-mortem showed the lesions of typhoid fever in the glands of the intestine, and a huge abscess about the cricoid cartilage. When the larynx

was split posteriorly the necrosed cartilage could be well seen, as shown in the specimens. (See Figure.)

CASE II.—H. N., aged seventeen years. The case was a typical one of typhoid fever; emaciation was extreme, diarrhœa profuse, delirium was severe and long continued. During the course of the disease numerous indolent abscesses occurred in various parts of the body. Typical rose-colored spots were numerous, spleen was enlarged, the temperature-range was typical.

Necrosed cricoid cartilage. *a*, necrosed cartilage.

Normal temperature was reached on the twenty-seventh day of the disease, and convalescence was uninterrupted for thirteen days. At that time the patient had a severe chill, apparently due to an exacerbation of a severe abscess in the arm. The evacuation of this abscess was followed by immediate fall of temperature. At the same time, when the patient was excited, he began to have stridulous breathing. When asleep, or when perfectly calm, there was absolutely nothing abnormal to be noticed about the breathing. There was no hoarseness, no soreness, nor swelling of the larynx externally.

Laryngeal examination at this time showed what was apparently a simple

laryngitis, simple redness of the mucous membrane of the larynx. This deceived me. I thought there was nothing but a catarrhal laryngitis. The next day, however, there was more or less stridulous breathing, which became marked during sleep. Operation was unfortunately delayed twenty-four hours, and in the meantime stenosis continued to increase, and the patient became the picture of distress, each inspiration being difficult and labored, before the surgeon was obtained.

Operation was decided to be done at 8 P.M. Owing to the wreck of the train bearing the surgeon, Dr. A. C. Wood, of Philadelphia, that gentleman did not arrive until 11 P.M. At 7 P.M. I was called to the house and found the boy suffering extremely, with a weak, unsteady pulse and in danger of suffocation. I was tempted, even with my lack of skill and dearth of proper instruments, to open the trachea before Dr. Wood's arrival. Fortunately, however, I desisted. Immediately upon Dr. Wood's arrival he opened the trachea; bleeding was profuse; the patient ceased to breathe; but by the skilful and fortunately rapid operation and artificial respiration the point of danger was passed and the tracheotomy tube inserted.

The patient wore the tube constantly for six months after the operation. Four weeks after the operation the lumen of the tube was occluded with gauze, at first for an hour, and later for the entire day, but invariably the obstruction was removed at night. Finally he slept with the tube occluded. The tube was first removed five months after the operation, but, after being out twenty-four hours, was replaced. It was finally removed six months after operation.

The patient remains well, with a slight stridor in breathing and hoarseness of the voice and some dyspnœa on exertion.

Dr. Charles P. Grayson, of Philadelphia, made examinations of the larynx from time to time, with the results as follows, which he has kindly allowed me to embody in my notes:

Previous to the laryngeal examination the association of marked inspiratory difficulty with a comparatively moderate alteration of the voice suggested a double abductor paralysis. The mirror, however, at once disposed of this suspicion by revealing an enormous swelling involving the tissues of the interarytenoid space and the aryepiglottic folds. It was a pale fluctuating mass in contact posteriorly with the pharyngeal wall, and extending forward almost to the base of the epiglottis. The space left for the ingress of air was extremely narrow and fully accounted for the dyspnœa. The patient's vitality was so low that puncture of the abscess without a preliminary tracheotomy would probably have proved fatal. During or shortly after the tracheotomy, which was performed the next day, spontaneous rupture of the abscess occurred, the point of rupture being upon the anterior surface of the swelling slightly to the right of the median line. During the ensuing several weeks moderate purulent discharge from this spot was accompanied by the escape of several small fragments of necrosed cartilage. Cicatrization

was attended with the development of a mass of exuberant granulation tissue, which was removed by the cutting forceps. In spite of frequently repeated dilatation of the glottis ankylosis of the crico-arytenoid joints occurred, and the present condition of the larynx is as follows:

Complete immobilization of the crico-arytenoid articulations and of the vocal cords. The latter are closely approximated in their anterior third, and then gradually recede from one another until at their posterior extremities there is an interval between them of about a fourth of an inch. The cartilaginous portion of the left cord is absent, owing to the destruction of the base of the corresponding arytenoid cartilage.

The points of greatest interest and importance in these cases seem as follows, and they are points noted in most published cases. In both instances the patients were convalescent. In one case the attack of fever was severe; in the other mild. In both cases the laryngeal symptoms appeared after some sort of exertion of traumatism; in the one eating an apple, in the other the shock of opening a rather large abscess. In both the severe symptoms came on suddenly and threatened life in a very few hours. Previous to the severe symptoms there was nothing which would alarm an observer who had not met with this extremely trying complication.

Early in the laryngitis in both cases there was some slight disturbance of breathing; in one some hoarseness; but in the first case these symptoms attracted absolutely no attention. I am quite sure the early symptoms in the second case would have gone unnoticed except for my experience with the first case. If that had been true the patient would doubtless have succumbed before he could have obtained relief.

In the case which recovered after operation I believe much benefit was derived after the operation from the daily plugging of the canula. In this way the cords were moved and not allowed to become fixed in adduction to so great a degree as otherwise would have occurred. Then, too, the patient became used to breathing with the tube closed, and there was no mental shock when it was finally removed.

Tracheotomy is the only possible relief, and should be done early —as soon as the diagnosis is made; indeed, now that surgical interference in typhoid cases is shown to be practicable, one had better err on the side of a useless tracheotomy than risk a sudden stenosis. I am sure all would agree to this if they could have gone with me through a few hours of this boy's life.

A CASE OF SCLERODERMA.

By SAMUEL B. WARD, M.D.,
OF ALBANY, N. Y.

On October 23, 1899, Dr. E. C. Van Dusen brought to my office Mrs. E. H., of West Athens, N. Y., that I might see her in consultation with him. As she was in haste to return home the examination was more or less hurried and unsatisfactory, and I saw her again at her home on November 3d. Her occupation was that of a housewife; she was forty years of age, born in Athens, N. Y., and had always lived there. Family history was negative.

Personal History. She was always strong and well as a child; her menstruation began at fourteen years of age, and was regular until January, 1900, when it ceased. She was married at twenty-two years of age, has had one child, and no miscarriages. In 1890 had an attack, the history of which sounds very much like that of appendicitis, followed by a copious discharge of pus from the rectum. She had repeated attacks of malaria until marriage; then she removed to a point three miles back from the river lowlands, and has had no paroxysm since.

In 1891 had an attack of pneumonia, severe in its character; crisis occurred on the tenth day, and recovery was complete.

Six years ago, in a runaway accident, was thrown out of a carriage and received a serious injury to her head; a slightly depressed circular scar, an inch and a half in diameter, remaining over the left frontal eminence, while over the right frontal eminence two lines of scar-tissue, crossing at right angles, mark the effect of the accident here. She was not unconscious, and, save the fright, showed no brain symptoms.

History of Present Illness. The first symptom the patient noticed was some thickening of the sternocleidomastoid muscles, which made movement of the head somewhat difficult. The patient next noticed that

the ends of the fingers of both hands seemed unusually white. Fingers felt cold to the touch, somewhat rigid, but not painful unless attempts at movements were made. Following this some stiffness with brawny infiltration over the wrists showed itself and made the movement of the wrist-joint difficult. The skin over the buttocks became somewhat thickened, and pain in the calves of both legs showed itself.

Examination, November 3, 1899: Patient is slightly built, rather emaciated, and looks anæmic. The skin of the face was of a yellowish color, fading away to a less dark hue on neck, while over the chest and abdomen no pigmentation can be seen. Over the knees and buttocks the skin seems slightly darkened in color.

When I visited her she was lying in bed, although she had been up the previous day and was intending to get up again after I left. Her pulse was 104 and her temperature 98.8°. Her hands were cold, but her feet were warm and somewhat moist with perspiration. The skin over the chest and abdomen was normal, but was markedly thickened over the wrist, less so over the hands and forearms. The skin over the back and buttocks was thick and leathery. She was cold and wanted the room warmer than was necessary for one in health. The lower extremities were both of them œdematous to a point half-way up to the knee, but not markedly so.

The face was quite expressionless, smooth like a mask, and her relatives had noticed this change. The nose was not changed at all. There was thickening of the skin on the forehead to a slight degree, but marked on the cheeks and temples, more so on the left side than on the right, destroying the symmetry of the face. Her tongue was pale and flabby, looking anæmic, and was slightly coated. The hair was soft and looked normal. The scars remaining from her accident of six years ago were distinct and showed no evidence of the thickening present elsewhere.

She could open her mouth barely wide enough to admit one finger. This seemed to be due to the pain which the effort produced in the masseter muscles. Taking food into her mouth caused great pain in the masseters before she began chewing it, which pain was not aggravated by mastication, but, on the contrary, gradually subsided.

The sense of taste was normal.

The pupils were normal, responding both to light and accommodation.

Examinations of the heart, lungs, and urine gave negative results. There is tenderness in the abdomen over the site of the appendix, which has been there ever since the attack she had in 1890. The spleen was slightly enlarged, while the liver-dulness was normal. Examination of the spinal column showed some tenderness over the spine on percussion in the lumbar region and also over the roots of the spinal nerves, on both sides, on pressure. Over the buttocks, pelvis, abdomen, and outer aspect of both thighs and left leg were numerous white striæ similar to those caused by stretching the skin, although there was no history of any swelling ever having occurred in most of these parts.

In the right upper extremity the limb was thin, but the skin was natural in appearance, except that just above the elbow it appeared somewhat reddened. Over the back of the wrist the skin was thickened and tough, not œdematous, but hard and brawny, and could not be pinched up; was not pale but mottled, as if the capillary circulation were imperfect; motion at the wrist was almost entirely abolished, and the effort to make motion, either active or passive, had been very painful, but at present it is less so.

There was no superficial hyperæsthesia or anæsthesia at this time, though she said that it had been anæsthetic. There was no pain in the wrist unless motion was attempted. Her hands were lying in a peculiar position indicative of helplessness. The wrist-joints were perfectly straight, neither extended nor flexed, as if the brawny swelling acted like a straight splint. Passing up from the wrist to the elbow this induration gradually disappeared. The skin over the back of the hand was about the same as at the wrist. The fingers were swollen up so that her wedding-ring, which six months ago almost dropped off, cannot now be removed without cutting it. The fingers were flexed in a curve, the effort to straighten them causing considerable pain and being only partially successful. It also caused the flexor tendons to stand out prominently on the anterior surface of the forearm. The true skin and the connective tissue beneath it seemed to be the seat of the thickening; the epidermis was not changed at all except by stretching. The wrist and all the joints below it seemed to be partially stiffened by disuse and became more flexible when they had been voluntarily moved or when passive motion was made for a few minutes. The left wrist and arm were in practically the

same condition, but slightly worse. The examination of the blood showed a condition of eosinophilia, for which table is appended.

Examination, February 13, 1900: The brawny induration of the face is very much less, so that the mouth can be opened and the tongue protruded, but in general the patient seems weaker. Over the wrists the induration is very much less, and the fingers have become thin and pointed. The hand is distinctly in the position of sclerodactylia. Over the knees the induration is marked and the legs are in a condition of semiflexion. In the region of the rectum the skin is hard, tensely drawn, and so firm that defecation has become difficult. Over the inner aspect of the lower portion of the thighs the skin is shiny, pigmented to a brownish color and seems much thickened. Over the olecranon process of the left ulna the skin is so tensely drawn as to be shiny and at the point of breaking. Over the styloid process of the radius the skin is so tightly drawn that it is perceptibly thinned and the bone is subcutaneous.

Examination shows the area of hepatic dulness to be increased downward.

The thyroid gland is evidently smaller than normal. No implication of other glands can be made out. The skin in which œdema has been present is now firm and tensely drawn and leathery, but devoid of œdema, the stage of atrophy having evidently set in.

Two or three weeks before death the urine became scanty in amount, high colored, and contained considerable albumin. Examination of the heart showed the presence of a loud, close-to-the-ear pericardial friction rub. Over the chest flatness developed. In the course of the following week the pulse became weak and rapid, and a marked general œdema showed itself. The heart-sounds became exceedingly faint, œdema of the lungs presented, the patient grew gradually weaker, and died on April 10th at 8 A.M.

Report of autopsy, made by Dr. George Blumer, director of the Bender Hygienic Laboratory, Albany Medical College, Albany, N. Y.

Autopsy done at West Athens for Drs. Ward and Neuman.

Mrs. E., aged forty years. Died 8 A.M. April 10th. Autopsy at 4 P.M. April 10, 1900.

Body 170 cm. long, slightly built, considerably emaciated. Rigor mortis present in the jaw, absent in the extremities. Post-mortem lividity of dependent parts. Skin of the legs to a point half-way up

the thigh is slightly discolored, being yellow, shiny in appearance, and having a stiff, leathery feel. The condition is most marked at the ankles and around the knees, and gradually fades away into proximally normal skin in the upper part of the thighs. A similar condition is present in the hands, forearms, and in the lower portion of the upper arms, and to a slight degree as far as the shoulder. The skin of the face is more markedly pigmented, being of a deep brownish-yellow, and the neck is also pigmented but less so than the face. The skin over the back and buttocks shows a similar stiffening, the only normal skin remaining in the body being that over the anterior surface of the thorax and abdomen. The arms and legs are held in a condition of semiflexion and cannot be extended. There are no glandular enlargements. Over the right internal condyle of the humerus is an irregular loss of substance 5 cm. in diameter, surrounded by bluish skin and with a base formed of granulation tissue. The same condition is present over the left internal condyle. The subcutaneous fat is small in amount. Muscles are atrophic and pale. There is slight subcutaneous œdema over the chest. The mammary glands are normal.

The peritoneal cavity contains 50 or 60 c.c. of clear serum, mostly in the flanks and pelvis. Both layers of the peritoneum are smooth. The omentum is delicate and free from adhesions. The appendix passes downward and inward across the brim of the pelvis and has a short mesentery to its tip. Length, 9 cm. Foramen of Winslow is open.

Diaphragm: On the right side at the fourth space, on the left side at the fifth rib.

The costal cartilages are not ossified.

Each pleural cavity contains about 1500 c.c. of slightly cloudy fluid. The pericardial cavity is distended with a cloudy, greenish fluid to the amount of 400 c.c. Floating in this are flocculi of lymph, and on the visceral surface a fibrinous false membrane is present in patches. A number of subpericardial hemorrhages are present.

The heart appears slightly enlarged. The left side is contracted, the right side flabby. The right side contains fluid blood and red and chicken-fat post-mortem clots. Endocardium and valves of right side normal. Average thickness of right ventricle 4 mm. Length, 8½ cm. Left side contains red post-mortem clots. Endocardium and valves

are normal. There are a number of adherent white ante-mortem thrombi in the apex of the left ventricle. The average thickness of left ventricle is 14 mm. Length, 8½ cm. Coronary arteries are normal. Heart muscle firm. On section pale and shows a faded-leaf appearance. The auricular appendages are empty. Foramen ovale is closed.

The left lung is free from adhesions. Pleura over the lower portion of the upper lobe shows a fresh fibrinous exudate. There is an old superficial scar at the apex. The anterior margin of the upper lobe is pale, cushiony, and emphysematous. On section slightly congested and slightly œdematous. The lower portion of the upper lobe and the entire lower lobe are airless and leathery in feel, slaty in color, and have the characteristic appearance of atelectasis. The mucous membrane of the bronchi is congested. They contain a little frothy mucus.

The right lung is free from adhesions. The upper lobe and the anterior portion of the middle lobe are emphysematous and pale, and on section as on the other side. The remainder of the lung is atelectatic. The bronchi and vessels as on the other side. One of the bronchial glands is enlarged to a diameter of 3 cm. and contains numerous large tubercles, some of them caseous, some calcareous.

The spleen is free from adhesions. Measures 14 x 7 x 4 cm. Capsule is smooth. Consistency is firm. On section the pulp is not increased. The trabeculæ and Malpighian bodies are easily visible.

The liver is free from adhesions. The average measurements are 25 x 16 x 10 The surface is smooth, mottled, of a reddish yellow color. Consistency is considerably increased. On section the centres of the lobules are congested. Peripheries are pale yellow.

The gall-bladder contains thick bile. The walls and mucous membrane are normal.

The left adrenal normal.

The left kidney: Capsule strips off fairly easily, occasionally tearing away a little kidney substance. The surface is smooth and mottled, of a yellowish-white color, with occasional discrete hemorrhagic areas. On section the cortex is markedly swollen and mottled like the surface. The cortex markings are blurred. The glomeruli are visible, at times pale, at times hemorrhagic. The pelvis is normal.

The right adrenal is normal.

The ureters are normal.

Right kidney same as left.

The mucous membrane of the bladder is pale, otherwise the organ is normal.

The vagina normal.

The uterus has a length of 8½ cm.

Endometrium is normal. The walls contain several pearly white, dense nodules with a striated cut surface, and varying in diameter from 3 mm. to 2 cm.

The Fallopian tubes are free from adhesions and normal looking.

The ovaries are fibroid, otherwise normal.

The mucous membrane of the rectum is pale.

The large and small intestines are normal.

The aorta shows a few patches of fatty atheroma.

The œsophagus is normal.

The stomach is dilated. The mucous membrane pale, somewhat thickened, and covered with sticky mucus.

Pancreas is normal.

The skin in the affected areas is thickened, but there appears to be no connective tissue infiltration of the subcutaneous connective tissue.

The thyroid gland is a little small, firmer than normal, and of a somewhat grayer color than normal. It apparently contains an increased amount of connective tissue.

One of the large peripheral nerves of the lumbar plexus showed no change to the naked eye.

Brain and cord not examined.

Anatomical Diagnosis. Scleroderma with pigmentation of the skin affecting the face, posterior part of the trunk and the extremities. Acute serofibrinous pericarditis with fatty degeneration of the heart muscle. Double hydrothorax with acute fibrinous pleurisy on the left side. Acute bronchitis with emphysema of the lungs and atelectasis of the lower lobes. Chronic passive congestion of the liver. Slight chronic passive congestion of the spleen. Subacute parenchymatous nephritis with hemorrhages. Multiple myomata of the uterus. Chronic interstitial thyroiditis. Tuberculosis of a bronchial lymph-gland. Small ulcers over the internal condyles of the humeri.

Bacteriological.

Cultures were made from the heart's blood, pericardium, lung, liver, spleen, and kidney. These were all negative except the cultures from the liver, which showed a number of colonies of a short, thick bacillus which decolorized by Gram, and which corresponded in its characteristics with the bacillus coli communis.

Microscopical.

Heart. The pericardium shows a considerable dilatation of the small bloodvessels, and accompanying this is a cellular infiltration of the superficial layers. No definite exudate can be seen in most of the section. In one or two places is a very slight amount of fibrin adherent to the surface of pericardium. The cells infiltrating the superficial layers are most of them of the type of round, lymphoid cells, though a few of them have the extra-central nucleus and the characteristic protoplasm of plasma-cells. A few polynuclears are also present. The connective tissue of the heart muscle shows a rather diffuse slight increase throughout the entire substance of the organ. This is rather more pronounced in the neighborhood of the bloodvessels, but is not by any means confined to their neighborhood. The newly formed tissue is in the form of rather loose-meshed connective tissue, most of the cells having the spindle shape of fully formed connective tissue cells. Sections stained with Weigert's stain for elastica show that with increase of connective tissue there is a distinct increase in the elastic tissue in the form of very fine fibres. The myocardium shows in places very distinct focal changes. These changes mostly occur in portions of the heart muscle lying nearest to the pericardium. The changes consist in the presence of areas of muscle-cells taking a refractive pink stain with the eosin, and which have lost their nuclei. These areas are infiltrated to a slight extent with polynuclear leucocytes. Aside from these areas the muscle fibres in the neighborhood of the connective tissue new formation are compressed, and in other portions of the heart muscle are areas in which transverse rupture of the muscle fibres has taken place either through the cement substance or through the muscle cell itself. The endocardium appears very slightly thickened in places, but in the main is normal. The bloodvessels of the heart show no distinct change.

Lung. The bloodvessels of the pleura are dilated and filled with blood. The pleura is infiltrated in places with some round cell, polynuclear leucocytes and an occasional cell of the plasma-cell type. The sections from the upper lobes of the lung show the alveoli much dilated, with thin walls, which are often broken into one another. The sections from the lower lobe show marked compression of the alveoli, which in places are almost entirely obliterated. Most of the alveoli in the upper part of the lung are empty. Those in the lower part contain a pink staining, almost homogeneous material, evidently corresponding to coagulated albuminous exudate. In some of the alveoli large dust cells can be seen. Bloodvessels of the lung are normal. There is a very small quantity of coal pigment present. Some of the bronchi show desquamation of their lining epithelium, and in some there is a small amount of exudate composed of polynuclear desquamated epithelial cells. The bronchial glands described under naked-eye appearances show only occasional areas of normal gland substance. The greater portion of the gland is occupied by larger or smaller caseous masses surrounded by a zone of epithelioid and lymphoid cells, and often containing giant cells, many of which have the typical Langhan's distribution of the nuclei.

Liver. Capsule is not present in section. The connective tissue of the organ is not increased. The central veins and their surrounding capillaries are in places dilated. There is a corresponding compression of the liver cells in these areas, and many of the compressed cells contain a granular yellowish pigment. The liver cells outside of these areas are swollen and granular looking, and occasionally show evidences of fatty change. Bile and bloodvessels appear normal. The blood in the capillaries contains an excessive number of polynuclear leucocytes.

Spleen. The capsule is not thickened. Trabeculæ not increased in amount. Pulp, Malpighian bodies and bloodvessels normal in appearance.

Kidney. Capsule is not present in section. Connective tissue of the organ shows very slight increase in a few places in the cortex. Both the glomeruli and the tubules in the cortex show very marked changes. These consist in an extensive infiltration of groups of tubules and of certain glomeruli, with very large numbers of polynuclear leucocytes. This infiltration is accompanied in the glomeruli

with great engorgement of the glomerular capillaries and an actual necrosis of entire loops of the glomerular capillaries, the necrosed portions taking a bright pink stain with eosin. The affected areas of tubules also show an extensive necrotic process, there being complete destruction of the lining epithelial cells over quite wide areas. This process is confined almost exclusively to the cortex, though present in a slight degree in the medulla. Bloodvessels of kidney show in places distinct thickening of the intima, in other places the walls of some of the smaller vessels are almost entirely necrotic and are infiltrated with polynuclear leucocytes. Large numbers of hyaline casts are present in the tubules in places.

The adrenal glands show no increase in connective tissue and are essentially normal.

Pancreas shows a slight increase in its interstitial tissue, usually in the form of fine bands of connective tissue between the groups of cells, and occasionally as a more diffuse process separating individual cells from one another. In the latter areas there is some compression and atrophy of the pancreatic cells, but for the most part the cells are normal.

Thyroid gland shows marked changes. These take the form of a great increase in the interstitial tissue of the organ, producing compression and atrophy of the glandular substance. The new-formed connective tissue is mostly in the form of a dense, fully formed fibrous tissue; but there are areas in which the thyroid tissue is infiltrated with small, round, lymphoid cells, apparently representing a fresh process. As in the heart muscle, there is a corresponding increase in the elastic tissue. The gland substance shows varying degrees of compression. In some places it has almost entirely disappeared over wide areas, in other places it is apparently but little affected. There is an abundance of colloid material in the slightly affected areas.

Uterus. Shows the presence in its walls of definite circumscribed tumor nodules, which are made for the most part of bands of smooth muscle running in various directions. In places running between the muscle cells are narrow bands of connective tissue. The larger nodules show areas of hyaline degeneration. The musculature outside of these nodules is normal.

The Fallopian tubes are normal in appearance.

The ovaries still contain a few Graafian follicles, but are largely fibrous.

The affected skin shows very marked changes. The horny layer is very thin. The epidermis is much compressed, narrower than normal. The papillæ of the papillary layer have almost disappeared and present themselves in places as slightly rounded, or pointed, downgrowths. There is a very marked increase in the connective tissue of the corium, which is continuous with a similar increase in the subcutaneous connective tissue. In the subcutaneous areolar tissue the strands of the connective tissue which are normally present are greatly increased in thickness. The increased connective tissue formation in the deeper layers of the skin has led to an almost complete disappearance of the appendages of the skin. Sebaceous glands are not made out in any of the sections. The sweat-glands, however, could still be recognized, though greatly compressed, and in places much distorted and with their coils spread apart by the new-formed connective tissue. The ducts of the sweat-glands can in places be made out much compressed, often deviated from their course. Hair follicles are in places present; they are also much compressed. The newly formed connective tissue is exceedingly dense, containing hardly any connective tissue cells, and being mainly composed of a fibrillated substance occurring in the form of coarse strands. The tissue is not of the same density throughout, being of a looser texture in the portion corresponding to the subcutaneous connective tissue than in that corresponding to the corium. As in the heart muscle and thyroid gland, the new-formed connective tissue is accompanied by a marked increase in the elastic tissue. In the corium it takes the form of very fine network, and in the subcutaneous tissue it occurs in much coarser strands. The peripheral nerves show marked increase in connective tissue in the form of an almost acellular fibrous tissue, and in this, again, the elastic tissue is also increased. The bundles of nerve fibres are markedly compressed. In sections stained with Van Gieson's stain many of the axis-cylinders have disappeared. The mammary gland shows a very marked increase in connective tissue. This tissue is of the same dense type seen elsewhere and has similar characteristics. It has led in many places to atrophy of the gland acini.

Revised Anatomical Diagnosis. Scleroderma with pigmentation of the skin affecting the face, posterior part of the trunk and the extremi-

ties. Acute serofibrinous pericarditis with acute myocarditis and diffuse chronic interstitial myocarditis. Double hydrothorax with acute fibrinous pleurisy on the left side. Acute bronchitis with emphysema of the lungs and atelectasis of the lower lobes. Chronic passive congestion of liver. Acute infectious nephritis. Multiple myomata of the uterus. Chronic interstitial thyroiditis. Chronic interstitial mastitis. Tuberculosis of a bronchial lymph-gland. Small ulcers over the internal condyles of the humeri.

Etiology. Scleroderma may occur at any age, a case having been reported by Cruse in an infant of three weeks, and one by F. Krüger in a man of seventy-five years of age. In Lewin and Heller's analysis it is shown that in childhood, from one to two years, the percentage of males to females is about equal, while in the next decade, ten to twenty years, the number of females, fifty-five, to the number of males, fourteen, shows that in the adult the female is much more frequently attacked. Boullier (quoted by Lewin and Heller) gives the percentage as 71 of all cases, and Lewin and Heller as 67 per cent. Uhlenhuth (in *Berlin. klin. Woch.*, March 6, 1899) gives 65 per cent. of all cases occurring in females. Hutchin (in the *British Medical Journal* for June 1, 1895), in an article on "Morphœa," divides it into three classes, and says that one of the classes occurs nearly always in adult women. As to races, cases have been reported in the negro, in the Chinese, in the Japanese, as well as in the white race. Of all nationalities the French have reported the greatest number of cases. It is probable that this disease is of nervous origin, and that the nervous instability of the French may account for the comparatively large number of cases reported by this nation. Psychical influences seem to exert a direct effect in its causation. H. F. Lawrence (*Intercol. Med. Journal*, Australia, July 20, 1898) reports a case of scleroderma diffusum following severe shock to the nervous system. Shaffer (*Verhandl. des 4 Congress d. Deutsch. Dermatol. Gesellsch.*) reports a case dating from the death of the patient's husband, while in a case of G. Lewin's symptoms began in a patient fourteen days after the suicide of her husband and death of her child. In a great number of cases exposure to cold is given as the immediate cause. In the case here reported the injury to the head may have been the causative factor in the commencement of the disease. Many cases have been reported in literature in which trauma has been described

as the causative factor in the production of scleroderma. In some cases rheumatism has been assigned as the cause of this disease, and this was the diagnosis in the case here reported before it was seen by me. The association of rheumatoid pains with scleroderma, and at times the arthritis present in this condition explains the frequency with which rheumatism in the older literature is ascribed as the cause of scleroderma. Dercum (in the *Journal of Nervous and Mental Disease* for October, 1898) reports a case of scleroderma with severe rheumatic arthritis involving nearly all the joints.

In regard to the symptomatology this case showed distinctly the three stages of, first, œdema; second, induration; and third, atrophy. In some portions of the body, as for instance the legs, œdema was present at the same time the wrists were in a condition of brawny infiltration, while over the face atrophy was occurring. The history of blanching and coldness of the extremities as an initial symptom is not unusual, nor is the condition of sclerodactylia exceptional; but in this case the sclerodactylia became less and less marked until toward the end the hands were not nearly as characteristic. The fact that throughout the course of the disease the eosinophile cells were increased so markedly is interesting, while the loss of the red cells shows disturbance of the circulatory medium.

TABLE OF DIFFERENTIAL BLOOD-COUNTS.

Date.	Number of erythrocytes.	No. of leucocytes.	Polynuclears.	Transitionals and large mononuclears.	Small mononuclears.	Eosinophiles.
November 3, 1899	4,280,000	10,000	64.25 p. ct.	8.4 per ct.	6.2 per ct.	21.15 p. ct.
February 13, 1900	300,000	12,000	62.4 "	4.6 "	8.6 "	25.4 "

The presence of the eosinophiles is rather interesting, and further study in this direction seems desirable.

Treatment. It is to be regretted that no line of treatment as yet suggested appears to have any permanent beneficial effect. In this case some of the remedies usually recommended gave temporary relief, but nothing more.

For making the blood-counts and other assistance in preparing this history I am indebted to my clinical assistant, Dr. L. H. Neuman.

APPENDICITIS IN TYPHOID FEVER.

By H. A. HARE, M.D.,
OF PHILADELPHIA.

My object in writing this very brief paper is to bring before the Association a clinical condition which I have met with with sufficient frequency to make me consider it by no means rare, and which has never failed to puzzle me. I refer to two groups of cases—namely those cases in which symptoms developing in the neighborhood of the appendix indicate the rapid development of appendicitis, yet in which these symptoms gradually subside and the patient gradually passes into an attack of typhoid fever. Secondly, I desire to speak of cases already well advanced in the progress of typhoid fever which develop appendicular symptoms.

The first group of cases is well represented by the following histories:

Case I.—A young man, aged twenty-one years, came under my care with a history that he had not been feeling well for several weeks, during which time he had some headache. He stated when first seen by the resident physician that he had pain in the left hypochondrium, but when I examined him the pain was chiefly in the right hypochondrium, and in the epigastrium, although the entire belly seemed unduly sensitive. Pressure upon the area of the appendix increased the pains already referred to, which, in my experience, is usually the case in appendicitis, and discovered excessive pain in the appendicular region. The temperature was slightly febrile, the pulse quick and fast, and the belly scaphoid. A rectal examination did not evince any pain in the neighborhood of the appendix seemingly, because the finger of the physician could not reach high enough. The next day the pain was markedly accentuated and more limited to the neighborhood of McBurney's point, and the belly wall was distinctly hard and board-like. I therefore asked Dr. Keen to see him, and he agreed that the symptoms were indicative, but as it was not convenient to operate at once, suggested that we wait until the afternoon.

A few hours later the symptoms seemed so typically those of appendicitis

that, as Dr. Keen was away, I asked Dr. Hearn to examine him. Dr. Hearn, in whose diagnosis we all have great respect, at once stated that the symptoms were typical, and agreed to operate; but just before the operation we both agreed that the patient's tongue looked somewhat typhoidal, and so postponed the operation once more, agreeing, in the meantime, that the treatment already instituted—namely, the administration of a mild saline and the use of an ice-bag over the appendix—be continued for another night.

I confess that this proposition did not seem to me a very wise one, for though I recognized the strong possibility that the case was one of early typhoid fever, this fact in no way appeared to me to modify the necessity for an operation for appendicitis: First, because it was perfectly possible that by coincidence appendicitis was complicating the onset of typhoid fever; and, again, it was possible that there might be typhoid infection of the appendix producing appendicitis—or, in other words, that the primary condition was due to the involvement of the alimentary canal in the pathological process produced by the bacillus of Eberth and particularly marked in the appendix. It did not seem to me that a suspicion of approaching typhoid fever negatived an operation, when everyone was agreed that the symptoms of appendicitis were present with sufficient severity not only to justify but to make necessary operative interference. I advanced these views to Dr. Hearn, who admitted that the symptoms were already severe enough to justify an operation, and who confessed that he had not a very good reason for refusing to perform it save that the possibility of a coming attack of typhoid fever might perhaps decrease the chances of recovery from the operation, and this feeling on his part, combined with the fact that I had seen such cases get well without operation, both when they were suffering from ordinary appendicitis and when complicated with typhoid fever, led me to agree to the postponement of operative interference.

On the following day the symptoms of appendicitis were no more marked than before, and, to state matters briefly, the symptoms of appendicitis gradually faded as those of typhoid fever became more and more accentuated, so that at the end of the week all of the symptoms of appendicitis had disappeared and typhoid fever was present in its fully developed form. I could cite several other instances, but this one and that which follows seemed to me sufficient as illustrating this type.

CASE II.—The second case was that of a boy of nine years, who was seized with a violent attack of pain in the lower right abdominal quadrant during a visit to the seashore. He was treated for this by rest in bed and the administration of purgatives, and on returning to Philadelphia ten days later, was again taken down with pain in the neighborhood of the appendix, the development of distinct muscular rigidity over the right side of the abdominal wall, a quick pulse, and pain also in the neighborhood of the right hypochondrium and epigastrium, which was increased by pressure over the appendix. In addition to the local symptoms, the general condition of the boy was that which indicated the presence of a grave illness, and I asked Dr. Musser to see him with me in consultation, Dr. Musser agreeing with me that the symptoms were obscure, but distinctly appendicular in type.

This case differed from the first in that the symptoms at no time were sufficiently severe to indicate an immediate operation. But they certainly were sufficiently marked to make us think strongly of sending for a surgeon in order that he might watch the case with us, and determine when it would be wise to operate. Here, again, in the course of a few days, under the use of an ice-bag, the appendicular symptoms disappeared, and the child passed through an attack of typhoid which, considering his age, was quite severe.

There are several points of interest in regard to these cases. In the first place, it is of interest that in a certain proportion of cases of typhoid fever the illness is ushered in by symptoms which are most marked in the right lower quadrant of the abdomen. Second, the interesting question arises as to the condition of the appendix and caput coli under these conditions. Third, the interesting question arises as to whether operative interference in these cases is necessary, and if operative procedures are instituted, whether they are advantageous or disadvantageous; and, finally, whether there are any conditions present in such cases which will enable us to state that the patient is suffering from a distinctly local lesion or from a general infection by the specific micro-organism of typhoid fever.

As I have stated in the beginning of my paper, I have now met with so many instances of appendicular trouble in the early stages of typhoid fever that I have come to regard it as by no means rare. In regard to the condition of the caput coli and appendix, it would seem probable that one or two conditions may be present. One of these is that of ordinary appendicitis, due to the pathological conditions which produce this disease, which happens to occur simultaneously with the

onset of typhoid fever, and the other is that the case may be one of those in which the early general symptoms are mild yet the intestinal lesions are marked. This condition is very well shown in the colored drawing which I show you, taken from a well-known atlas of pathology by Kast and Rumpler. In this illustration we see how ulceration in the neighborhood of the caput coli could very readily produce great tenderness, abdominal resistance, and other local symptoms closely resembling appendicitis. In other words, I believe that in such a case the physician must make a differential diagnosis between true appendicitis and the condition represented in this illustration. The question arises as to how this may be done; and that it must be done is evident, because in the case of ulceration of the caput coli operative interference is not only useless but dangerous, chiefly because of the shock to the patient's system when he is already suffering from a grave infection. I must confess that I do not believe that there are very definite clinical symptoms which will enable us to make the differential diagnosis, and I am inclined to believe that much importance should be paid to the results of examining the blood. From what we know of leucocytosis we can rest assured that in ordinary cases of appendicitis the white blood-corpuscles will be considerably increased, whereas, on the other hand, it is a well-known fact that in typhoid fever they are not increased. And, therefore, in all probability typhoidal ulceration in the neighborhood of the caput coli, while it might produce the ordinary subjective and objective symptoms of appendicitis, would not show distinct blood changes. This was the case in the first patient that I have spoken of to-day. An examination of his blood failed to reveal any leucocytosis, and this was considered by us as an important diagnostic aid. That this aid cannot, however, always guide us is proved by still another case in which the symptoms of appendicitis developed much later in the course of typhoid fever than in the two cases just described, the patient being in the third week of the disease before the positive evidences of an appendicular abscess were present. During the whole course of his illness this patient, who was a middle-aged man, complained of more or less pain in the right side of his abdomen, which was often most severe almost as far up and as deep in the back as the posterior portions of the liver and kidney. Finally, after a marked chill, distinct bulging, not only in the neighborhood of the appendix anteriorly, but posteriorly over the pelvis,

with slight œdema on deep pressure, forced us to operate, and no sooner was an incision made in the abdominal wall than a pint and a half of extremely fetid pus escaped, which contained staphylococci and the bacillus coli communis, but in which the micro-organism of typhoid fever was not found. In this patient there was a very slight leucocytosis, not sufficiently marked to justify us in positively stating that there was an acute inflammatory complication of the typhoid process, and yet the white cells were sufficiently increased to prevent us from ignoring the change in their number.

It has generally been held by physicians and surgeons within the last few years that the presence of a rapid pulse, a scaphoid belly wall, distinct muscular resistance and violent pain were all of them symptoms demanding operative interference for appendicitis. And I do not think that the mere possibility of the patient being about to pass through an attack of typhoid fever is any reason in itself for refusing the patient operative relief, although I recognize, of course, that the development of typhoid fever immediately after such an operation is a grave complication.

I regret that this paper must be more suggestive that positive in its conclusions. My own feeling is that these cases of appendicitis in the early stages of typhoid fever are even more difficult to advise than ordinary cases, which are certainly difficult enough, and I am, as I have already stated, at a loss how to proceed when I meet with them in practice. Were it not for the results of examining the blood I should feel myself still more uncertain.

VARIETIES OF BACILLUS DIPHTHERIÆ.

By F. F. WESBROOK, M.D., LOUIS B. WILSON, M.D.,
AND
O. McDANIEL, M.D.

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The great variability in morphology and staining reaction of bacillus diphtheriæ is perhaps its most striking characteristic. It is puzzling to the beginner, and to those with most experience brings an occasional feeling of discomfort where quarantine is dependent upon the report made. In the bacteriological examination of clinical cases, notwithstanding the extreme variation in the picture seen, there are usually certain well-recognized forms which soon become familiar.

A complete description of the various factors taken into consideration by a bacteriologist in arriving at a diagnosis is almost an impossibility. Account is taken of size, relation of thickness to length, irregularity of shape and staining reaction, and relation of the bacilli to each other (*i. e.*, arrangement).

These various points probably appeal to different laboratory workers with unequal force, and it is conceivable that one observer is willing to include certain bacterial forms as diphtheria bacilli because they show polar granules, whilst to another their departure from his recognized limits of shape, size or arrangement prevents such inclusion. Or, conversely, arrangement or relation of the bacilli to each other appeals so strongly to one person that he recognizes certain forms as diphtheria bacilli, which to another are of such a size, or shape, or display such staining characteristics as to be ineligible for such classification.

Whilst in routine initial examinations of clinical cases it is probable that the percentage of disagreement in diagnosis between people accustomed to such work is small, in later examinations of the same cases

for release from quarantine and in the investigation of diphtheria-like micro-organisms derived from healthy throats, noses or other sources, there is room for greater diversity of opinion. In the former case, perhaps, there is the unconscious bias afforded by the presumption of a pathogenesis in the micro-organisms found. From the public health stand-point, it seems justifiable, where diphtheria-like micro-organisms are found in a culture from a throat, nose or other site which shows some evidence of a pathological condition not incompatible with diphtheria infection, to assume that such bacilli are the cause of the morbid condition, and, furthermore, that they are possibly dangerous to other human beings as well as to those in whom they are found. In the other class of examinations where clinical symptoms, if present originally, have long since abated, or where evidences of diphtheria infection have been entirely wanting, there is opportunity for a great variety of opinion of which full advantage has been taken. A study of the literature of the subject will show that each different aspect of morphological and staining reaction has had its supporters as being all important, though the endeavor has been made to co-ordinate each of these aspects or groups of them with certain cultural, biochemical or pathogenic properties.

It is obvious that if in order to make certain diagnoses in doubtful cases there be required for each micro-organism a complete study of its characteristics in pure culture the acquirement of data must be extremely slow. Inability to investigate a very large series of cultures derived from a large number of people at the same time and under like conditions will preclude the early arrival at any definite general conclusions regarding such forms as diphtheria, pseudo-diphtheria, xerosis and other allied forms of bacilli.

This conflict of opinion as to the possibilities and methods of differentiation of bacillus diphtheriæ from allied or pseudo forms becomes daily more serious, since health boards are coming almost universally to depend for their guidance in restrictive and quarantine methods upon the data afforded by bacteriological examinations.

The experience of the laboratory of the Minnesota State Board of Health has been, if at all different from that of other laboratories, in degree rather than in kind so far as meeting with diphtheria and diphtheria-like bacilli in situations where they were unexpected. In 1896, upon the request of the authorities of the Minnesota State

Public School for Dependent and Neglected Children, an investigation was begun to determine the cause of diphtheria and sore throat which had been more or less endemic for ten years. In that investigation it was found that the bacilli met with could be roughly divided into two classes, called in the preliminary report and earlier communications "typical" and "atypical" diphtheria bacilli.[1] The former were granular and irregular bacilli, such as would be commonly recognized by all bacteriologists as diphtheria bacilli. The latter were probably for the most part "Hoffmann's pseudodiphtheria bacillus," though many cultures of this form derived from various sources were then and have since been proven to be virulent, and, further, it has been repeatedly shown that immunity to them is possible by the use of commercial diphtheria antitoxin.

Sometimes the bacilli were found mixed both in clinical diphtheria and in seemingly healthy throats. Sometimes one class would appear to be present as the sole diphtheria-like organism, and sometimes the other. This was true of both clinical cases and healthy children. Continued investigation developed the fact that at one time 75 per cent. of the children (263) were infected in either nose or throat.

The "typical" bacilli were present in the nose in 38 per cent. of all infected children, and in the throat in 30 per cent. The "atypical" forms were more numerous still. This was at a time when no clinical diphtheria had occurred for some months. The children were placed in complete individual isolation and treated in order to rid their throats and noses of all suspicious forms. This wide-spread infection was so striking that it seemed well to make investigations to determine whether like conditions could be found elsewhere in the State. Accordingly, within the last three years at various times the flora of the noses and throats has been examined in:

(*a*) The State Institution for the Feeble-minded some two or three months after a mild outbreak of sore throat.

(*b*) Various town and country day schools. In some instances diphtheria was present in the town or village at the time of the investigation. In others no history of possible diphtheria infection in that

[1] British Medical Journal, April 16, 1898. "A Preliminary Communication on Bacillus Diphtheriæ and its Variants in a School in which Diphtheria was Endemic." Transactions of the American Public Health Association, 1899, vol. xxv. "Studies on the Distribution of Certain Varieties of the Diphtheria Bacillus."

locality for a period varying from some months to years could be obtained.

(*c*) Bethany Home, Minneapolis, where women are received before and cared for during and for a period of at least a year after confinement. Here the child population is, of course, very young. At the time of the taking of the cultures (249) there were three cases of diphtheria in the home.

In these examinations there has been considerable variation in the percentage of infection with diphtheria-like bacilli. It may be mentioned in passing that, as a general rule, the noses are more frequently infected than throats with diphtheria-like bacilli, though the number of species of associated bacteria is less in noses than in throats. In "Homes," where all the inmates are housed together, the percentage of infection is higher than in day schools. Where diphtheria has been recently or is at the time prevailing, the percentage of infection of healthy individuals is higher than where such infection has been for a long time absent.

The ordinarily recognized forms of diphtheria bacilli are more frequently found in the throat than in the nose. The findings in the Maternity Home, where nurses, mothers and babies were all examined, were nearly the same as in the State Public School for Dependent and Neglected Children. Discussion of these results will be reserved for a future occasion.

Attempts have been made to secure pure cultures from as many such sources as possible for study, and at various times from 100 to 300 such cultures have been under investigation at once.

In the endeavor to obtain some definite idea as to the morphological, staining, cultural, biochemical and pathogenic properties of such large numbers of cultures, it will not appear strange that difficulties have been encountered which have augmented with the increase in material, and even more so by the accumulation of data derived from their study. At first, critical of the data afforded by other observers, in which it seemed absolutely impossible to systematize results so as to recognize and differentiate the various forms, we were not long in finding such extreme difficulty in getting an idea of whither our own work was tending that we were compelled to begin afresh. In recording the forms and staining reaction met with alone, it was found that carefully written records a few weeks or months old con-

veyed very little impression of the types of bacilli met with. Our original plan of subdivision into "typical" and "atypical" forms of diphtheria bacilli was found to be almost as far from sufficiently minute and accurate as had been the classification of other observers into "diphtheria," "pseudodiphtheria," "xerosis," etc. We were forced some months ago to adopt some more accurate means of recording our observations on morphology. In the study of the morphology of pure cultures in most instances, especially where they have been derived from typical clinical cases of diphtheria, it is the exception to get even a moderate degree of uniformity in the general shape, size, staining reactions, etc., of the individual bacilli, whilst to get complete uniformity is not to be hoped for.

It seems impossible, without actually watching under the microscope the development of a colony from a single bacillus, to be certain that a culture has been derived from an individual micro-organism because of the strong tendency of the bacilli to cling together. It is, therefore, ordinarily impossible to know in any case whether the various forms met with in a pure (?) culture are derived from one or several parents. In all our studies, pure (?) cultures were obtained by sowing a minute quantity of the first mixed culture from the throat, nose, etc., into broth, which was then vigorously shaken. From this immediate sowing was made upon Löffler's serum by careful "streaking out." From one of the most symmetrical of the resulting isolated colonies fresh broth was again inoculated and the shaking and "streaking out" repeated. This process was gone through with from three to fifty times during a period of from a few days to nearly three years. It is probable that some if not all of these cultures have sprung from individual bacilli.

At first it seemed possible by obtaining an accurate description and colored sketch of all the bacilli in each pure culture to arrive at a classification. Upon becoming gradually accustomed to close observation, and particularly when it came to sketching the forms, it was soon found that one or more forms might be common to several cultures whose general morphological characteristics seemed to be and were quite different. By general morphological characteristics is meant the general picture seen by a trained observer. In ordinary routine examinations the observer is influenced perhaps more than he always realizes by the presence of certain forms which meet his par-

ticular views in regard to type, and may overlook or minimize the importance of other to him less well-known forms which may be present.

Attempts to classify types of bacilli on the appearance of microscopic fields of presumably pure cultures had to be abandoned, and, instead, we were compelled to adopt a classification based on the morphology of individual bacilli.

The reasons for this are obvious from the study of the tables of observations. The arrangement here presented is purely an arbitrary and provisional classification of the morphological types encountered. As made originally, the water-color sketches to which your attention is called[1] and which form the basis of the classification were made to scale (magnification of 20,000 diameters) from the pure cultures just mentioned. Within the last six months it has been found necessary to add new types as they came to be recognized by special training in the adaptation of this method of record to the tabulation of the results.

As the ordinary method of diagnosis of diphtheria is by the microscopic examination of twelve to twenty-four-hour Löffler's serum cultures which have been stained by Löffler's methylene-blue, these types have been sketched from cultures of this age stained by this method. The serum used was prepared in the ordinary way except that it contained 1.25 per cent. glycerin and was both coagulated and sterilized in the autoclave.

The bacilli were measured accurately and sketched with the camera lucida. From these the water-color sketches were enlarged to scale, the details being filled in by direct microscopic study of individual bacilli.

Groups of Types.

As will be seen in the sketches, the bacilli met with are divided not only according to size and shape, but into three main groups depending on their staining reactions.

GROUP I. *Granular Forms.*—These show distinct spherical, ovoid, or markedly rounded granules. These forms are represented by the

[1] From the water-color sketches exhibited at the meeting, Plates Nos. I. to VI. were reproduced. The reduction has been to ¼ scale, thus making the magnification as shown in the plates 5000 diameters.

plain letters, A to G. In each variety except B the granules show metachromatism—*i. e.*, take a reddish tint with fresh Löffler's methylene-blue. The granules are, as a rule, at one or both poles of the bacilli, though they may occur elsewhere also. The protoplasm of the bacilli not included in the granules varies in intensity of staining, though it is always lighter in color than, and usually in marked contrast to, the granules. In this group, forms A to D inclusive are ordinarily recognized as bacillus diphtheriæ. Branching forms, when granular, should be here included, although not represented in the plates.

GROUP II. *Barred Forms.*—Here, as in the granular forms, the irregularity of the staining is the distinguishing characteristic. Bacilli belonging to this general class present a distinct barred appearance as of an actual removal of segments of protoplasm. The darkly staining portions vary in the intensity of coloration in different bacilli of the same variety and even in the same bacillus. Their size and shape are variable, though, as a rule, not spherical nor ovoidal like the granules in Group I., and the color, whilst usually dark, does not suggest metachromatism.

The lighter places in many bacilli show a distinct though very faint blue coloration, whilst in other individuals the appearance is more like a string of irregular cocci or bacilli. The relative size of the dark and light areas is also variable. The number of the dark segments varies from three to nine. Often in the bacillus composed of three segments one light band occurs near the middle, dividing it into two nearly equal portions, one of which is again subdivided. Such an appearance is suggestive of the origin of the bacillus from one of the varieties included under Group III., by a process of subdivision of one of the component portions of the diplobacillus.

Whilst in Group II. will be recognized some types familiar to all as diphtheria bacilli—*e. g.*, type A^1, B^1 and C^1—many of the more regular forms—as D^1 and E^1—are not to be distinguished from those described by certain authorities as xerosis bacilli. It will be noted that this group of type forms is not so complete as Groups I. and III. This is because in this laboratory barred forms co-ordinate in size and shape with F and E have not been observed. Should they at any time be found, the types F^1 and E^1 will be added to the group.

GROUP III. *Solid Color Forms.*—These include not only the

solidly staining forms of all shapes and sizes, but also those with the appearance of diplo-bacilli. The former, perhaps more especially the larger forms, would be acceptable to the majority of observers as diphtheria bacilli. The latter were formerly included for the most part by us under our "atypical" forms, and have been looked upon as pseudodiphtheria bacilli by Hoffmann and others. It seemed better to place them in this group than with the barred varieties, because the paired arrangement is so frequent that we were at first inclined to believe it to be constant in some strains. The intensity of coloration varies in different bacilli in the same variety, and there may be some shading in the same individual.

Types in Detail.

TYPES A, A^1 and A^2. (See Plate I., Figs. 1, 2, and 3.) These are ordinarily described as involution forms. Here are included those swollen "bizarre" bacilli which appear as spherical, semilunar, "dumb-bell," "Indian-club" and "ghost" forms. Portions of certain of these may be as much as 3 microns in diameter, though usually 1 to 2 microns thick by 3 to 6 microns long. Many, if not all of these, may be found in:

(*a*) Direct smear preparations from clinical cases.

(*b*) Either young or old cultures made directly from clinical cases as well as from healthy individuals.

(*c*) Either young or old cultures which have been kept in the laboratory for many months, derived originally from clinical cases or from healthy people.

In view of these facts their inclusion amongst "degeneration or involution" forms is questionable.

The distinction between A and A^1 is rendered somewhat difficult at times by the occurrence of barred varieties containing one or more metachromatic polar granules. In all three types there is the greatest variability in the staining reaction, causing some difficulty in diagnosis. No one of the types represented can be considered an impossible form of bacillus diphtheriæ when occurring with the others. Certain of them—in type A^2—if found as the only microbe present, besides staphylococcus or streptococcus, in a throat culture would not suggest a diagnosis of diphtheria.

In these types the adoption of a single form as the type of the

group which governs the classification elsewhere has been purposely avoided. Their one common characteristic is their swollen appearance. The virulence of these three types to man is probable from their frequent great abundance and almost constant presence in small numbers in all cultures derived from clinical cases. They are, however, rarely or never the predominating types in pure cultures which have been shown to be virulent to animals.

TYPES B, B^1 and B^2. (See Plate II., Figs. 1, 2, and 3.) Types lettered B, B^1 and B^2 are also by some observers spoken of as "involution" forms, and by many others as "attenuated" forms. They are long and slender (about 0.5 micron in thickness and 3 to 7 microns in length) while the granules in B and the segments in B^1 usually have the longitudinal diameter considerably greater than the transverse. The granules in B rarely, if ever, show metachromatism, and do not swell the body of the bacillus. This type (B) has been found as almost the sole diphtheria-like organism present in a series of cultures from a case of typical clinical diphtheria and proven to be highly virulent to guinea-pigs.

Types B^1 and B^2 have not been found as the predominating forms in direct throat or nose cultures, though sometimes present in small numbers. It will readily be seen from the resemblance in size and shape of type B^2 to various common bacteria of the mouth that it would be very unsafe to diagnose this type as bacillus diphtheriæ except when it occurs as a variant in pure cultures.

TYPE C. 0.5 to 1 micron thick by 3 to 6 microns long. (See Plate III., Fig. 1.) (The usual length of 4 microns may be increased to 6 microns in those forms which seem to be about to divide.) Often somewhat curved forms, in which protoplasm stains light blue except always at poles and occasionally at one point between the poles, where rounded, rarely ellipsoid granules occur. These granules show metachromatism—*i. e.*, stain dark blue with a marked reddish tinge, and are thicker than the rest of the bacillus.

This form is the most common one met with in clinical cases, and may be considered the "long" form of bacillus diphtheriæ, as contrasted with the "short" form of most observers.

TYPE D. 0.75 to 1 micron thick by 2 to 3 microns long. (See Plate IV., Fig. 1.) Similar in most respects to C., but shorter and thicker and apparently straighter.

PLATE I.

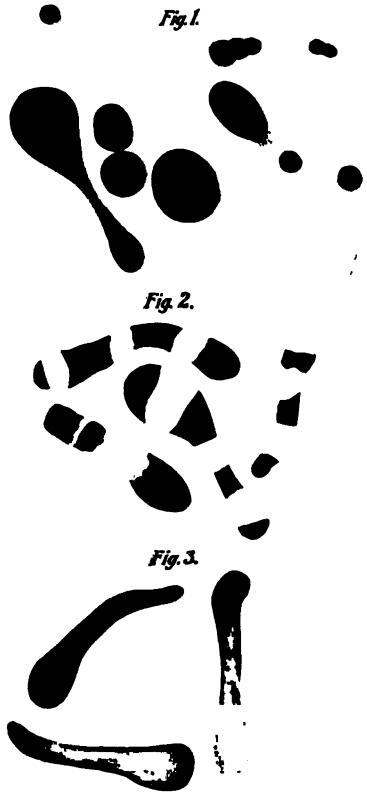
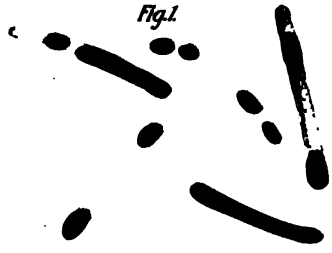
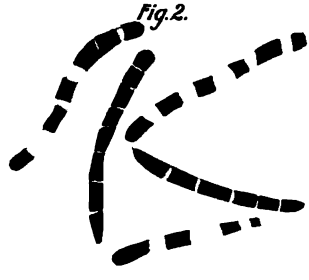


FIG. 1. Type A. 1 to 2 μ thick, 3 to 6 μ long.
FIG. 2. Type A^1. 1 to 2 μ thick, 3 to 6 μ long.
FIG. 3. Type A^2. 1 to 2 μ thick, 3 to 6 μ long.

PLATE II.





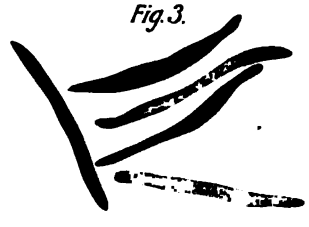


FIG. 1. Type B. 0.5 μ thick, 3 to 7 μ long.
FIG. 2. Type B^1. 0.5 μ thick, 3 to 7 μ long.
FIG. 3. Type B^2. 0.5 μ thick, 3 to 7 μ long.

PLATE III.

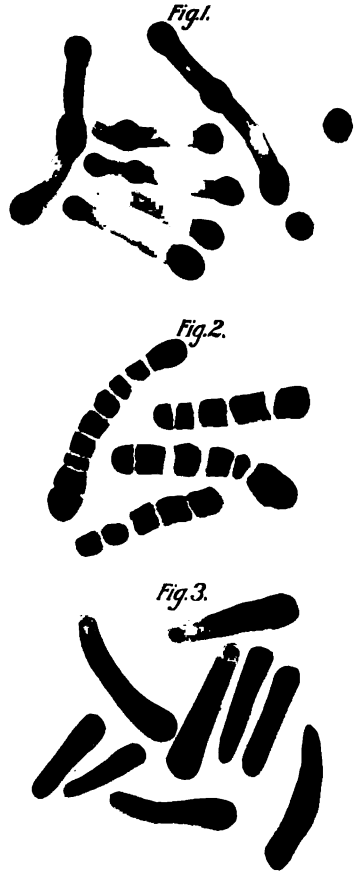


FIG. 1. Type C. 0.5 to 1 μ thick, 3 to 6 μ long.
FIG. 2. Type C^1. 0.5 to 1 μ thick, 3 to 6 μ long.
FIG. 3. Type C^2. 0.5 to 1 μ thick, 3 to 4 μ long.

TYPE E. 0.5 to 0.75 micron thick by about 1.5 microns long. (See Plate V., Fig. 1.) Otherwise like D. D and E comprise probably the "short" forms of bacillus diphtheriæ of other observers.

Though types C, D and E are ordinarily diagnosed without hesitation as bacillus diphtheriæ, yet when considering them in relation to the other types herewith described, it must not be forgotten that they are frequently met with in the throats or noses of perfectly healthy persons not recently exposed to clinical diphtheria. Further, they sometimes fail to show any degree of toxicity when tested on guinea-pigs.

TYPE F. 0.25 to 0.5 micron thick by 1 to 2 microns long. (See Plate VI., Fig. 1.) Small, slender bacilli with tapering extremities. The bacilli stain light blue and contain one or two rounded granules of an intense dark blue with a reddish tinge—*i. e.*, metachromatic. The granules occur at one end or near the middle, or in both places. The granules are thicker than the rest of the protoplasm which tapers from their point of occurrence toward the ends. This form is extremely rare, and its pathogenesis has not yet been studied.

TYPE G. 0.5 to 0.75 micron thick by 1 to 1.5 microns long. (See Plate VI., Fig. 3.) Shortest granular form. Bacilli usually paired. Each pair resembles a dark-blue ellipsoid divided transversely by a clear, narrow space. Granules are very small, difficult to see, and occur only at the distal extremities of the pairs. They stain an intense blue, and occasionally show a slight trace of red. Has been very rarely found in clinical cases, though its pathogenesis for guinea-pigs has been shown in cultures from a non-clinical case.

TYPE C^1. 0.5 to 1 micron thick by 3 to 6 microns long. (See Plate III., Fig. 2.) Long curved forms usually thicker at one end, or straight forms thicker in the middle, with bluntly pointed ends. Its characteristic is a dark-blue color with four to eight lightly stained or white transverse bands.

In the experience of this laboratory this form, so commonly figured in text-books as the type, is not so frequently found as the larger forms with polar granules.

TYPE D^1. 0.5 to 1 micron thick by 2 to 3 microns long. (See Plate IV., Fig. 2.) As compared with C^1 this form is shorter, has fewer bands and is usually straighter.

TYPE E^1. 0.5 to 0.75 micron thick by 1.5 to 2 microns long.

(See Plate V., Fig. 2.) Otherwise, like D^1, except that staining is more frequently lighter.

TYPES C^1, D^1 and E^1 have been described by numerous observers as xerosis bacilli, although the occasional etiological relation of C^1 to clinical diphtheria is fairly well established.

TYPE C^2. 0.5 to 1 micron thick by 3 to 4 microns long. (See Plate III., Fig. 3.) Curved or straight forms, usually slightly clubbed or tapering at both ends. Stains a fairly uniform intense blue, no metachromatism; granules and barring absent. Infrequently met with, but up to the present time never found by us as the predominating form even in pure cultures which have been long under study. Its virulence to man and animals is, therefore, a matter of conjecture alone.

TYPE D^2. 0.75 to 1 micron thick by 1 to 2.5 microns long. (See Plate IV., Fig. 3.) Bacilli generally present the appearance of pairs with opposing extremities flattened and thickened. Whether the light or colorless portion seen between is unstained protoplasm in a long bacillus or an actual space between two opposed bacilli cannot yet be stated. It is probable that one condition is succeeded by the other, since solid bacilli of the same shape, length and thickness are always present in pure cultures which have been repeatedly sown from isolated colonies, and are included in this type. The distal extremities of the paired forms are bluntly pointed or abruptly rounded. All bacilli stain a fairly intense even blue. Metachromatism is absent.

This is the type to which particular attention was drawn in a former communication as the "atypical" form of B. diphtheriæ.[1] It is the most prevalent form at Owatonna, is occasionally the only form present in clinical cases, and is frequently pathogenic to guinea-pigs. When so, protection is afforded by the use of commercial diphtheria antitoxin.

TYPE E^2. 0.5 to 0.75 micron thick by 1 to 2 microns long. (See Plate V., Fig. 3.) Very like D^2, except that it is smaller and apparently straighter.

D^2 and E^2 are probably included under the "pseudodiphtheria" or "Hoffmann" group of bacilli of other observers. They are frequently found together. Frequently each occurs in pure cultures without admixture with other forms. This is true also of direct

[1] British Medical Journal, April 16, 1898.

PLATE IV.

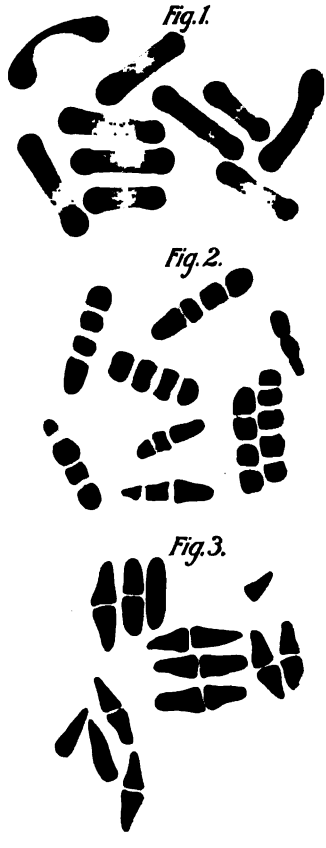


FIG. 1. Type D. 0.75 to 1 μ thick, 2 to 3 μ long.
FIG. 2. Type D^1. 0.5 to 1 μ thick, 2 to 3 μ long.
FIG. 3. Type D^2. 0.75 to 1 μ thick, 1 to 2.5 μ long.

PLATE V.

FIG. 1. Type E. 0.5 to 0.75 μ thick, 1.5 μ long.
FIG. 2. Type E^1. 0.5 to 0.75 μ thick, 1.5 to 2 μ long.
FIG. 3. Type E^2. 0.5 to 0.75 μ thick, 1 to 2 μ long.

PLATE VI.

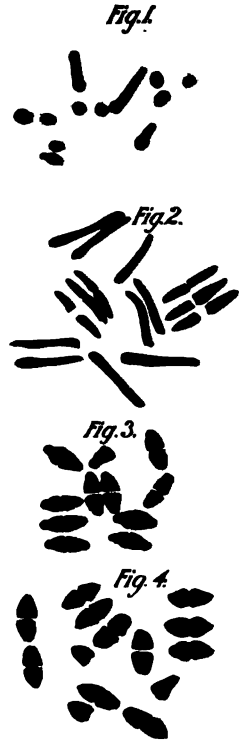


FIG. 1. Type F. 0.25 to 0.5 μ thick, 1 to 2 μ long.
FIG. 2. Type F^2. 0.25 μ thick, 1 to 2 μ long.
FIG. 3. Type G. 0.5 to 0.75 μ thick, 1 to 1.5 μ long.
FIG. 4. Type G^2. 0.5 to 0.75 μ thick, 1 to 1.25 μ long.

throat or nose cultures. The pathogenesis of E^2 yet remains to be determined.

TYPE F^2. About 0.25 micron thick and 1 to 2 microns long. (See Plate VI., Fig. 2.) Small slender bacillus with one or both extremities tapering. Stains an even, usually light blue. Frequently arranged in pairs like D^2 and E^2. A rare form, and one which like B^2 would not be recognized as related to diphtheria in throat cultures, but only so when found as a variant in pure cultures.

TYPE G^2. 0.5 to 0.75 micron thick by 1 to 1.25 micron long. (See Plate VI., Fig. 4.) A bacillus resembling D^2 and E^2 in staining and arrangement, but shorter. Has almost diplococcus appearance and resembles E, except for the presence of granules.

Variations in Type.

The study of variations in types is complicated by the fact that there is usually admixture of types in both original and pure cultures. Attempts have been made to determine the *sequence* of forms:

(*a*) In cultures derived from clinical cases for routine diagnosis for establishment and maintenance of quarantine.

(*b*) In cultures from throats and noses of healthy children under complete individual isolation.

(*c*) In pure cultures isolated as previously described.

(*a*) After the first positive report is given in a clinical case the patient is supposedly placed in complete individual isolation. The maintenance of strict isolation in private families is, of course, difficult, and usually abundant opportunities are given for the transfer of bacteria from attendants and surroundings to the patient. Consequently such transfer cannot be absolutely excluded as the possible cause of the appearance of new types of bacilli in the patient during the course of the disease. The disturbing factor, however, is probably very seldom actually operative, as will appear from a study of the following clinical cases:

CASE No. 1 (E. S., No. 8166).

Exam. No.	Types present.	Exam. No.	Types present.
1	C, D, E.	5	C, E, A, D.
2	A, D, C.	6	D, E, A, E^2, D^1.
3	A, C, D.	7	B^1, D^1, E, D, A, D^2.
4	C, A, D.	8	D^2, D^1.

CASE No. 2 (W. D., No. 8181).

Exam. No.	Types present.	Exam. No.	Types present.
1	C, A, D.	3	E^2, C, D, A, D^2.
2	C, D, A, E.	4	D^2, E^2, D^1, C^1, D, A^1, G^2.

Cases Nos. 1 and 2, in which the cultures were taken during a period of about three weeks, show (*a*) the presence of large granular types, with absence of other types during the prevalence of clinical symptoms, and (*b*) the entire replacement of granular types by barred and solid types as convalescence was established and just prior to the entire disappearance of all diphtheria-like organisms. This seems to be the usual order of variation in clinical cases, as has been noted by other observers and frequently in this laboratory.

That exactly the opposite conditions may obtain is shown by the following:

CLINICAL CASE No. 3 (R. S., No. 7693).

Exam. No.	Types present.	Exam. No.	Types present.
1	D^2, E^2.	4	D, D^2, E^2.
2	D^2, E^2, D^1, E^1.	5	D, C, A.
3	D^2.	6	D, C, E, A.

Here it will be seen that with the onset of symptoms only solid types of bacillus diphtheriæ were present, and that not until the fourth culture—third week of the disease—did the granular types appear. They then became and remained the only types found until the final entire disappearance of all diphtheria-like organisms. Such cases in the experience of this laboratory are infrequent, but that they do occasionally occur is beyond question.

(*b*) Variations in the types found in a series of original throat or nose cultures from children, even under complete individual isolation, may be more apparent than real. In complete individual isolation there is no opportunity for the introduction of other forms from other persons. It must be remembered, however, that there is no possibility of determining definitely the flora of the entire body of the patient himself. An examination of the throat is not an exact index of the various types to be found in the nose. When both nose and throat show the forms in synchronous cultures, the Eustachian tube, the eye, skin or other portions of the body may prove to be the source of subsequent invasion by other types. Notwithstanding these difficulties, since knowledge of the morphological variation of bacillus diphtheriæ within the human body seems so important, every op-

portunity for such study should be embraced. This requires the observance of the most careful technique. Portions of the patient's body not being examined must be kept as clean as possible by frequent bathing and by the use of antiseptic solutions. The cultures must be taken over all accessible portions of the throat, nose, eye, etc. Care must be taken to avoid any fluctuation in the medium, in the temperature and period of incubation and in the details of staining. The cover-slip preparation must contain material from all portions of the culture, and must be patiently and carefully searched. The "personal equation" should be eliminated as far as possible by having all the observations of a series made by the same microscopist.

Examinations of 189 cases, made so far as possible under the above conditions, have failed to show such great variation due to accidental causes as might have been expected on theoretical grounds. A few cases will serve to illustrate results obtained. The types are indicated in order of their predominance in the slide examined.

CASE No. 4 (H. C., No. 3683, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	E^2, G^2, F^2.	5	E^2, D, E, E^1, D^1, C^1.
2	E^2, D^2.	6	E^2, F^2.
3	E^2, D^2.	7	E^2, D^2, D.
4	E^2, D^2, D, C.	8	E^2, G^2, E^1, D^1, D^2.

It will be seen here that E^2 was the predominating form throughout. D^2 was present in all cultures except the first and sixth. Variation to other solid forms occurred three times, to barred forms twice, and to granular forms but once.

CASE No. 5 (C. A., No. 2918, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	E^2, G^2, D^2, B^2.	3	E^2, G^2, E, G.
2	E^2, D^2.	4	E^2.

Here, again, E^2 was the predominating type in all cultures. It was associated with closely related solid forms three times, and granular forms occurred but once.

CASE No. 6 (M. J., No. 50, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	D^2, E^2, G^2, D^1, E^1.	4	E^2, G^2, D^2.
2	E^2, D^2.	5	E^2, G^2, D^2, F^2, F.
3	D^2, E^2, E^1.	6	D^2, E^2, C^2.

Here D^2 and E^2 were present throughout and alternated in predominance. Other closely related solid and barred forms were present five times, and a granular variety but once.

CASE No. 7 (E. A., No. 1078, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	E^2, D^2, E^1, D^1.	5	D^2, C^2.
2	E^2, D^2, A^2.	6	E^2, D^2, C^2.
3	D^2, E^2, D^1, B^1, A^2, C^2, B^2.	7	D^2, E^2.
4	D^2, E^2, A^2.		

In this case D^2 was prominent throughout, while the variation was only to other solid forms and twice to closely related barred forms.

CASE No. 8 (A. C., No. 3975, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	E^2, D^2, E^1, D^1, C^1.	4	E^2, F^2, E^1, D^1.
2	E^1, D^1, E^2, D^2, C.	5	G^2, E^2, E^1.
3	B^1, D^1, E^1, F^2.		

This case presents a marked predominance of barred types with some variation in each culture to closely related solid types.

CASE No. 9 (L. C., No. 1136, McD.).

Exam. No.	Types present.	Exam. No.	Types present.
1	C, D, E, A, B^1.	5	E, F, C, B^1, C^2, C^1, E^2, F^2.
2	B^2, C^2, C^1, C.	6	D, C, E^2, F, B.
3	E, C, B^1, B^2.	7	D^2, C, D, E, F^2, F, G^2.
4	C, D, E, F, E^2.	8	E^2, E, D, C, G.

In this case granular types are in marked predominance with C and D as the leading types. Variation, however, is very great, ranging in the granular group from the largest to the smallest (A to G), and to barred or solid types in every culture.

This serves to illustrate the fact, frequently observed, that the variability of the granular types of bacilli is greater than that of the solid forms.

(*c*) Twenty pure cultures isolated from various sources by streaking out from selected single colonies as each subculture was made have been selected as illustrating the variation in type in serial examinations of pure stocks. The results have been tabulated and are presented in the accompanying table of "Morphology."

This table is too voluminous for anything more than a few generalizations, and a better understanding of the matter will be arrived at by the selection and careful study in detail of a few of the stocks.

OF MOR

WATONNA).

7097 1894	2852	4296 McD.	2629 McD.	7067	W.
G² G E² F E D²	C D E²	D² E²	G² E²	E² F E D¹	D²
.....e (?)	None (?)	Staphylococci	Staphylococci	Staphylococci	None (?)
G G² ² G²	E² G²	D² E² G²	D¹ B¹ D² A	D² G²	D²
GG² E² D D¹	D B¹ D¹	D B¹ B G²	D² D	D² G²	D² E² G²
D² G ² G²	C D B¹ D¹	E² D² G²	E E² D² G²	E D² G²	D² G² E²
G ² D E	F²	E² D²	E² G²	D² G²	E² D²
G D E	C D E A	D² E D¹	E² D²	E² G²	G² E²
E² ² G²	E E² B¹	D² G²	E²	G² E²	G²
G² G F D B¹	D² B¹	D² E²	E² G²	E² G	E² G²
No growth B¹ D¹	D² D¹ B¹	E²	E²	Contaminated	E² D²
E² G² ² G² D¹	E² G²	D² B²	D² B²	D² B²	E² G²
No growth G D¹	D F A	No visible growth	D² G²	No visible growth	No growth
No growth G D¹	D² E	D² B¹	G² D² B²	G² D²	No growth

PURE STOCK, No. 1. (Clinical Case, No. 3834.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat culture	C, D, E, E^2.		
2. Pure culture* . . .	B, C, A.	C, D, A.	B, C, A.
3. " " . . .	B, D, D^2.		C, D, E.
4. " " . . .	C^1, D^1.		
5. " " . . .	D, E, G, C.		
6. " " . . .	D^2, E, C^1.		
7. " " . . .	D^2, C^1.		
8. " " . . .	A, C, B.	C, C^1, A.	

It is interesting to note that in this stock, type C, originally the predominating form, was still present two years later, though with it were the so-called "attenuated and swollen involution forms" B and A. To regard them in this case as involution forms is unwarranted when it is seen that the stock reverts to the shorter granular, barred and solid types, though A and B are again present in the last examination of the young serum cultures. It will be noticed that on one occasion the barred or "xerosis" forms, C^1 and D^1, were present without admixture with other types, though no barred forms were present in the original culture. This is of interest, because this stock originated from a virulent clinical case in which the bacilli persisted for a long time in the throat. It has proven virulent for guinea-pigs in every one of many inoculations.

Type C, or one of its nearest neighbors amongst the long types in the accompanying sketches, was present in every examination. The presence of C did not seem to be influenced by the age of the culture at the time of examination.

PURE STOCK, No. 2. (Clinical Case, No. 3837.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat culture	C, D.		
2. Pure culture† . .	B, C^1, C, D^2.	B, C, C^1, A.	B, C, C^1, A.
3. " " . . .	D, E, B, D^2.		C, D, E, A, C^1.
4. " " . . .	B, C^1.		
5. " " . . .	A, D, E.		
6. " " . . .	B, A, C, C^1.		
7. " " . . .	B, C, A, C^1.		
8. " " . . .	A, C, B.	C, C^1, A.	

In this stock only one solidly staining type (D^2) was found present, and that only on two successive occasions, and then was less numerous

* Two years after isolation.

† Two years after isolation.

than the other forms. The general tendency is to the predominance of the long forms throughout. The culture has remained virulent for guinea-pigs throughout its whole history, and was obtained from a severe clinical case.

PURE STOCK, No. 3. (Clinical Case, No. 6175.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat cultures	D, E^2.		
2. Pure culture* . .	D^2, C^2.	G^2.	D^1, D^2, D, A^2.
3. " " . . .	D^2, E, C^2.		
4. " " . . .	D^2, E^2.		
5. " " . . .	D^2, G^2, G.		
6. " " . . .	D^2, E, E^2.		
7. " " . . .	D^2, C^2.		
8. " " . . .	F, E^2,	D^2, G^2.	

In this stock the persistent predominance of the solid types (D^2 and E^2) is very marked, though almost every culture shows short granular types (usually considered non-virulent) present. This is of special interest since the stock is from a clinical case and proved to be pathogenic to guinea-pigs whenever tested.

PURE STOCK, No. 4. (Non-clinical Case, No. 4303, McD.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat culture	C, D.		
2. Pure culture† . .	D, F, D^2, C.	D, B, A.	B, A, C^1.
3. " " . . .	C, D, E.		C, D, E, A.
4. " " . . .	B, A.		
5. " " . . .	A, B.		
6. " " . . .	C, D, A.		
7. " " . . .	B, C.		
8. " " . . .	A, D, D^2, E^2.	D, E, C^1, A.	

Though this stock was obtained from the throat of a child who at no time gave any evidence of clinical diphtheria, had not been exposed to clinical diphtheria, and at the time of taking the culture was in complete individual isolation, yet the original and almost every subculture of it showed only granular types—*i. e.*, those usually considered as diagnostic of diphtheria. The stock is virulent to guinea-pigs. This stock is of peculiar interest, since, except for the entire absence of clinical symptoms in the patient, it would have been impossible at all times to have differentiated it for diagnostic purposes from Stock No. 2 (from a marked clinical case).

* About one year after isolation. † Nine months after isolation.

PURE STOCK, No. 5. (Non-clinical Case, No. 5218, McD.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat culture	C, D, E^2.		
2. Pure culture* . .	B, C, C^1.	C, D, E, A.	B, C, A.
3. " " . .	C, D, E, E^2.		C, D, E, A.
4. " " . .	A, B, C, D, E, E^2.		
5. " " . .	A, C.		
6. " " . .	A, C, D.		
7. " " . .	C^1, B, A.		
8. " " . .	C, D, C^1, A.	D, C^1, E, A.	

This stock also was obtained from a child without clinical symptoms of diphtheria, not recently exposed to diphtheria, and under strict individual isolation when the culture was taken. The large granular types are present and predominating, but it has not been possible to kill guinea-pigs with this stock with large doses of grown cultures.

The similarity of the predominating granular types in Stocks Nos. 2, 4 and 5 is remarkable when considered in connection with their great dissimilarity in virulence. Thus, No. 2 is from a clinical case and is highly virulent to guinea-pigs; No. 4 caused no symptoms in the child-host, but is virulent to guinea-pigs; No. 5 caused no clinical symptoms and is not at all virulent to guinea-pigs. We seem to have here three distinct grades of virulence without any corresponding change in morphological type.

PURE STOCK, No. 6. (Non-clinical Case, No. W.)

	16 to 18 hours.	40 to 45 hours.	90 hours.
1. Original throat culture	D^2.		
2. Pure culture† . .	D^2.	D^2, E^2, G^2.	D^2, G^2, E^2.
3. " " . .	E^2, D^2.		G^2, E^2.
4. " " . .	G^2.		
5. " " . .	E^2, G^2.		
6. " " . .	E^2, D^2.		
7. " " . .	E^2, G^2.		
8. " " . .	D^2.	D^2, E^2.	

This stock was obtained from the throat of one of the writers soon after a short visit to the State Public School, where bacteria of the types found were present in many noses and throats. A slightly reddened, swollen sore throat was the reason for taking the original culture. These symptoms quickly subsided, and the bacteria disappeared, under treatment with antiseptic gargles, from the throat within

* Eight months after isolation. † One year after isolation.

a few days. It will be noted that at no time in the history of the stock were other than solid types (D^2, E^2, G^2) present, yet the cultures readily killed unprotected guinea-pigs, while others of the same size and weight remained alive and well after synchronous injection with large quantities of the bacteria mixed with commercial antitoxin. It would thus appear that the stock is true diphtheria, though it caused but slight symptoms in man and is of the morphological type described by many observers as "pseudodiphtheria."

When the observations here recorded were begun, the stocks had been isolated by a repetition of this process of colony picking and subsequent "streaking out" from three to fifteen times. Each subculture having been made in the same way, it is apparent from the tables* that the stocks at the time of the last observation had been subjected to this purification process from twenty to forty or more times.

Assuming that where the initial throat cultures were mixtures of different groups of types, it might be expected that in most of such stocks a single type or its neighbors within the same group would have been the result of the long-continued selective process, and this has been found to be true. Examinations of the later cultures of most of the stocks show that, as a rule, some and generally all of the types met with in the original throat cultures are found again late in the series of examinations. If not grouped in one specimen, as they were in the original throat or nose culture, all of the original types are usually found present scattered throughout the later cultures. To illustrate, when we have granular and solid types in the original culture we rarely find, so far as can yet be determined, permanent disappearance of one of these initial types in the later examinations.

It appears that the granular types when predominating or unmixed with the barred or solid types in the original cultures have, however, a tendency, as in throat cultures taken in series, to become more and more mixed with or replaced by barred or solid forms altogether in the later examinations. Insufficient data is available to warrant any such positive statement at the present time.

Certain of these stocks, however, in which one of the solid types is the only diphtheria-like organism seen in the original throat culture, and in which the immediately succeeding subcultures show only solid

* The tables presented at the meeting were much more voluminous than those here given. Tables were also exhibited there which are not given here at all.

types, are found to contain later in the series some of the barred or granular types and seem to show a gradual transition from solid types through barred to granular types.

Whether a parallelism really exists or not between variations in type as they occur in series of pure cultures or in throats from day to day cannot be definitely stated, though such would appear to be the case.

In general it may be stated that in successive cultures of any stock in which the isolation method employed would lead one to expect the loss of certain forms originally present, all are, on the contrary, usually preserved. Notwithstanding the fact that with the types originally present there may occur later other types in the same or different groups, there is a strong tendency to preserve some one or two types throughout the series.

Recording Observations in Routine Examination for Diagnosis.

It is hoped that the adoption of the uniform system of recording observations in routine examinations may ultimately result in the solution of several etiological problems. There is given below the results of the examination of the original throat cultures from the last hundred cases of clinical diphtheria on which positive bacteriological diagnoses were made in this laboratory.

	Cases.
Granular types alone present	42
Barred " " "	0
Solid " " "	8
Mixture of granular and barred types present, solid types absent	8
Mixture of granular and solid types present, barred forms absent	30
Mixture of barred and solid types present, granular types absent	1
Mixture of all three types	11
Total	100

The granular types will be seen to be most numerous, and 91 per cent. of the cases showed their presence, though they were present without admixture of other types in but 42 per cent.

The barred types were never found alone, but in mixtures of types were present in 21 per cent. of the cases. The solid types were present as the sole discoverable form of diphtheria bacillus in but 8 per cent. of the cases and in mixtures of types in 50 per cent.

So far as these examinations can be relied upon for proof of the etiological relation existing between the various types and clinical

diphtheria, it would seem that the granular forms are much more frequently the cause of clinical diphtheria, C and D being by far the most common forms found. C and D were found occurring together in 61 per cent. of the cases. D was found in 78 and C in 63 out of the 91 cases in which the granular forms occurred, so that when C was present it was mixed with D in 61 out of 63 cases.

Relation of Cultural to Morphological Peculiarities.

An extended series of observations on the cultural characteristics of various pure stocks has been made. Parallel sowings were made on all the ordinary culture media and on various modified forms of blood-serum. The full discussion of these observations would much exceed the limits of the present paper.* It may be sufficient to note here that the variations in cultural characteristics are almost as great as those in morphology, though in general they are embraced within the limits of the results hitherto obtained by other observers. The extreme difficulty of maintaining a given type free from admixture with other types has necessitated most of the observations being made on groups of closely related types rather than on a single one. Where this has been the case stocks containing the same predominating types gave similar cultural appearances, the slight variations being, perhaps, due to the dissimilarity of the subordinate morphological types in the stocks.

A full discussion of this series of observations must be reserved for a future communication.

Pathogenesis to Man and Animals, and Quarantine Regulations in Relation to Morphological Types.

Further than the brief mention given to these points in the preceding portion of the paper, little need be said.* Variation and mixture of types are constantly found, and unless the associated types be closely related, we cannot assume at this stage of our knowledge that everyone of the types represented would be virulent if found alone, even when the culture is obtained from a severe clinical case or proves fatal to guinea-pigs. This must be the case unless we are prepared to admit that anyone of the types here classified is capable of change into or replacement by anyone of the other types.

* Tables illustrating these points were exhibited at the meeting.

If it be admitted, for instance, that any of the already well-recognized types may change into A, as would appear to be the case from its general acceptance as an involution form, where must the line of possible variation be drawn? G and G^2 would appear to be beyond all possibility of inclusion as diphtheria bacilli, but in one experiment when these types were present in one of our carefully isolated pure cultures, without other detectable admixture, on inoculation into a guinea-pig, death was produced in less than forty-eight hours, and the culture isolated from the site of inoculation showed forms D^1 and a few D^2 as the only diphtheria-like organisms.

In quarantine measures, if the bacteriological method be employed, it must combine speed with accuracy.

Morphology and staining must continue to be, perhaps, the most important basis of diagnosis. But these recognize only one variable factor, viz., the bacilli, and ignore the local and general resistance of the host.

In general, then, we are driven to dependence upon the association of clinical symptoms and any of these forms when it is the predominating form of microbe in the throat.

Summary.

1. The routine bacteriological diagnosis of diphtheria for establishment and maintenance of quarantine must continue to depend largely on the observation of bacilli in 12 to 24-hour serum cultures from the throats of patients.

2. The great variety of forms met with in such cultures—some of them virulent and others not—is bewildering even to the best-trained diagnosticians.

3. Our present methods of describing the forms met with are inaccurate, incomplete and unintelligible to others.

4. To overcome this difficulty there is submitted a detailed description and arbitrary classification of types of known and probable diphtheria bacilli as observed under all conditions on Löffler's blood-serum and stained with Löffler's methylene-blue.*

* Roux's, Ernst's, Crouch's and Neisser's methods, and a number of modifications of them, have all been tested in this laboratory, and all of them abandoned in favor of Löffler's method for routine diagnostic work, since, while all of them possess certain special advantages, none of them gives as much data concerning mixed cultures as does Löffler's stain when properly used.

5. This classification places all types in three general groups: (*a*) Granular, (*b*) barred, and (*c*) solid (or evenly staining) forms. Each group is divided into types based on the shape and size of the bacilli.

6. A study of variations in the sequence of types in series of cultures derived from clinical cases of diphtheria shows that:

(*a*) Granular types are usually the most predominant forms at the outset of the disease.

(*b*) The granular types usually give place wholly or in part to barred and solid types shortly before the disappearance of diphtheria-like organisms.

(*c*) Solid types, by many observers called "pseudodiphtheria bacilli," may cause severe clinical diphtheria.

(*d*) Solid types may sometimes be replaced by granular types when convalescence is established and just before the throat is cleared of diphtheria-like bacilli.

7. A study of variations in the sequence of types in a series of cultures in the throats and noses of healthy but infected children under complete individual isolation shows that:

(*a*) The variability of granular types under such conditions is greater than that of the solid or barred types.

(*b*) Any type in marked predominance at the beginning is likely to persist as the predominating type for a long period of time.

8. A study of a series of subcultures from a number of pure stocks shows that:

(*a*) There is a strong tendency for a type present in the original culture to persist even for a number of years.

(*b*) Types not found in the original culture, but closely related to types there present, may later in the history of the stock appear, disappear and again reappear.

(*c*) This variation may be not only in types of the same group but also to types of similar size in other groups—*e. g.*, the variation of granular to barred and solid types and the converse.

(*d*) This variation may be so complete as to entirely change the predominating types present in the stock.

9. In a hundred clinical cases selected at random the first throat cultures showed granular types present alone in 42 cases, solid types alone in 8 cases. The remaining 50 cultures were mixtures.

10. Comparable cultural variations were obtained in a long series of sowings on ordinary media and special serum mixtures.

11. In the present state of our knowledge, data for the establishment and maintenance of quarantine must be obtained from the clinical symptoms as well as from the bacteriological findings.

DISCUSSION.

DR. ABBOTT: It is manifest to everyone present who is familiar with bacteriological technique that Dr. Wesbrook's paper represents an enormous amount of work, and from what we have heard has led to rather confusing results. Until we know definitely the normal morphology of this organism I do not see how this confusion can be obviated. We call it a bacillus, but from the number of observations that have been made it is very questionable if this is really its morphology. While the object of Dr. Wesbrook's work is evident, still I do not believe it possible to establish any constant connection between the various forms of micro-organisms seen by him and the clinical character of the disease from which they were obtained. I think if one examine various cultures of diphtheria bacillus carefully one would readily encounter practically all of the forms depicted by Dr. Wesbrook, and often all of them in a single culture. My belief is that many of them are simple involution forms, and I know that many of them can be produced at will by alterations in the environment under which the micro-organisms are cultivated. It must be admitted, however, that diphtheria bacilli found in the throats of individuals where strong disinfectants have been used, as well as those found late in convalescence from the disease, do often show alterations that can leave no doubt as to their being in a state of degeneration, this degeneration being doubtless due in the one case to the action of the germicide, and in the other case to the germicidal activity of the recovering tissues. One point in particular to which Dr. Wesbrook has made reference I think of importance, and that is occasional finding of virulent diphtheria bacilli in the throats of healthy individuals. In a few instances this has given rise to doubt as to the etiology of this organism in the production of the disease, but this is a one-sided view of the matter. We know that a specific, pathogenic organism is not capable of producing disease under all conditions. It produces disease only in susceptible species and in individuals who are at the time of its invasion susceptible to its pathogenic activities. This question of infection cannot be viewed from one side alone; it must always be considered from the stand-points of direct causative factor and of individual invaded. When virulent diphtheria bacilli are present in the throat of a well individual it can be explained in only one way, namely, that at the time that individual is not susceptible to its action; but from the public health stand-point it must be borne in mind that that individual, as well as convalescents from diphtheria, and individuals suffering

from very mild manifestations of the disease, are a very grave menace to the health of those with whom they come in contact, for, because of their mildness, they usually escape the sanitary control that they would otherwise receive. In consequence, all cases of this kind in which diphtheria bacilli are found are now regarded by boards of health as subject to their supervision, and while this ruling unquestionably causes inconvenience to the individual, still it is for the benefit of the public.

DR. PARK: Such bacilli as those on the last line, with their typical forms but with a faint and even stain, I have never met in pure culture. In almost any culture, however, some having these characteristics will be present. I have regarded them as bacilli which have passed their prime, and as, therefore, not taking up the stain well. In the diagnostic examinations at the New York Health Department we regard any culture which contains only bacilli of the form G^2 as having pseudodiphtheria bacilli only, and as giving no more reason for the isolation of the person from which it was made than if it contained cocci only. The form E^2 we regard as suspicious in character, and when we find it not accompanied with more characteristic forms we either ask for another culture from the throat or plate the bacillus out and test it.

Even in regard to bacilli with the characteristic form of the upper two rows, we never can absolutely tell in any given case whether they are virulent or not. From a case showing characteristic lesions or giving a history of contact with a true case of diphtheria, we may be almost certain of their virulence, but bacilli of the same characteristic appearance from doubtful cases should be tested for their virulence, whenever they persist long after convalescence. We tested recently such bacilli from the throat of the wife of a Rochester physician, and they proved not to be virulent. She had been isolated and her house placarded for three months. Numerous similar but less striking cases could be noted. These bacilli were probably non-virulent. In our experience bacilli which at the beginning were virulent continue virulent so long as they remain in the throat.

The presence of these characteristic bacilli in the throat secretions of healthy and slightly diseased and convalescent persons presents a condition which at the present time is beyond our powers to properly handle. These bacilli undoubtedly are often virulent, and when they are communicated to others they may incite disease, and yet to make cultures from certain throats and because we find the bacilli, to insist on isolation of their owners, while we purposely avoid making cultures from throats equally liable to contain bacilli, seems hardly fair. We, in fact, hardly want to know of all of the throats containing virulent bacilli, since we fear we would not be able to enforce isolation. At the Foundling Asylum, where in the past diphtheria so frequently followed measles, they now, instead of making cultures regularly, immunize every case with antitoxin so soon as the Koplik spots are noticed. Since this practice was started diphtheria has been eliminated as a complication of measles.

DR. WESBROOK: In attempting to summarize this paper in the time to which I felt entitled, owing to the congested condition of the programme, to give clearly in a few words its salient points, has been impossible. Had time permitted its reading, several of the points brought forward by Drs. Abbott and Park would have been found already discussed. As I stated in my attempted synopsis, the basis of the paper is the morphology of the diphtheria bacillus, and at this time it was impossible within the limits of the paper to go into the cultural characteristics or the matter of virulence; and in order not to go to any length into the question of the relation of the various types of bacilli to public health, I will just read this extract from the paper. (Here followed the reading of the two paragraphs of the paper "Relation of Cultural to Morphological Peculiarities," and "Pathogenesis to Man and Animals and Quarantine Regulations in Relation to Morphological Types.")

The fact that the types have been selected from cultures grown for the same length of time (eighteen hours) upon the same medium, and that observations on many of the cultures have been extended for a number of years, would seem to eliminate the possibility of one type being simply a developmental stage of another single type.

Dr. Abbott's suggestion concerning the differences between the past and present methods of preparing culture serum, and the possibility of this difference being effective in producing previously observed types cannot, of course, be overlooked. Our serum, however, is always prepared in the same way, and the observations in any series are made upon cultures grown on one lot of serum—*i. e.*, prepared on the same day. It would appear then that the influence of environment can be eliminated in the production of variation so far, at least, as any one series of observations goes.

In answer to Dr. Park's skepticism concerning whether certain forms—(*e. g.*, A^2 and B^2) if met with in purity—are to be considered as diphtheria bacilli, I may say that they have never been met with as the only type present, and would be considered diphtheria bacilli by us only when met with as variants in cultures containing other and more commonly recognized types.

In fact, with the exception of perhaps D^2 and E^2, it rarely or never happens that we obtain any type without admixture of other types. This, of course, complicates the matter of determining the pathogenic properties of any given type. Pathogenesis of a given bacillus for a guinea-pig, or lack of it, does not necessarily serve as an index of possible virulence for the human being, although unfortunately it is the only test we have.

PROLIFERATION AND PHAGOCYTOSIS.

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(*From the Sears Pathological Laboratory, Harvard University Medical School.*)

The effect which injurious agents, especially the toxins secreted by bacteria, produce on tissues is manifested in four different ways:

1. By degeneration or necrosis of cells;
2. By exudation from the bloodvessels;
3. By proliferation of cells; and
4. By phagocytosis; the latter term is used here to mean the inclusion and digestion of certain cells by other cells.

These four processes may occur separately, or in various combinations and proportions. The first two processes are generally accepted and taught. It is in reference to the last two, proliferation and phagocytosis, that I wish to present a certain amount of evidence bearing on the character of the cells involved, on the nature of the toxins which excite the processes, on the duration and termination of the lesions, and on the relation of the processes to repair.

The view that toxins can cause various cells to proliferate, and certain cells to become phagocytic for other cells, was first forcibly called to my attention by a histological study of the lesions of typhoid fever which I published in 1898. Since then I have studied these processes in various diseases in nearly a thousand autopsies occurring at the Boston City Hospital during the last three years.

What I wish to show is that strong toxins cause degeneration or necrosis of cells and exudation, while dilute and weak toxins produce proliferation and phagocytosis. In support of this hypothesis I will cite in part the result of the study of large numbers of cases of certain diseases, in part a limited number of typical and of unusual lesions.

Certain organisms, such as the staphylococcus pyogenes aureus and the bacillus diphtheriæ, produce strong toxins which act quickly, and

chiefly locally; the effect on the tissues is to produce necrosis and exudation. Other organisms, such as the bacillus typhosus, produce mild toxins which act slowly, and produce proliferation or phagocytosis or both. The stronger toxins, however, can produce these same processes of proliferation and phagocytosis when sufficiently dilute.

The best example I have found of this was in the kidneys of a girl, five years old, who died after four days from an acute myositis of the right thigh due to the staphylococcus pyogenes aureus. The autopsy was made one hour post-mortem. The femur was not affected. There were multiple miliary abscesses in the lungs, heart, and kidneys. In the kidneys they occurred for the most part in the pyramids, especially toward the bases. Very few of the foci were softened; most of them consisted of areas of necrosis with more or less infiltration with polynuclear leucocytes. Judged by inoculation experiments in rabbits, the lesions were not over forty-eight hours old.

Many of the lymphatics adjoining these beginning abscesses and running toward the bases of the pyramids were dilated and filled with numerous large phagocytic cells, together with a few lymphoid and plasma cells and polynuclear leucocytes. The inclusions in the phagocytic cells consisted principally of polynuclear leucocytes and lymphoid cells.

Careful study of these lymphatics showed occasional mitosis of the lining endothelium, and much more frequently migration of the endothelial cells through the walls into the adjoining connective tissue. The endothelial cells pass through the wall of a lymphatic in exactly the same way that the polynuclear leucocytes do, namely, a process of the nucleus surrounded by a minimum of protoplasm pierces the wall first, and the rest of the nucleus and the protoplasm gradually follow. After the endothelial cells contained inclusions they still showed the changes of form characteristic of amœboid motion, but none was found in the act of emigration.

In diphtheria the chief lesions are focal and occur for the most part in the air-passages in the immediate vicinity of the bacillus diphtheriæ; but there are other lesions due to the diffusion of a small amount of the toxin through the blood and lymph circulations. The most interesting of the latter are found in the lymph nodules of the tonsils, spleen, and gastro-intestinal tract. They consist of a moderate proliferation of the cells lining the reticulum. This proliferation

usually occurs in the centres of the lymph nodules, but sometimes is diffuse or eccentric. Even more marked than the proliferation is the incorporation of the lymphoid cells of the lymph nodules by the cells lining the reticulum and by the new cells formed from them. Phagocytosis like proliferation usually begins in the centres of the lymph nodules and spreads peripherally, but may occur diffusely. In advanced lesions all or nearly all of the lymphoid cells in a lymph nodule may be destroyed. In such cases the centre of a lymph nodule shows a clump of epithelioid cells with the protoplasm more or less fused together and containing no inclusions, because all of the incorporated cells have been digested, and others are not within reach. Toward the periphery phagocytic cells containing partially digested cells are found, while at the periphery the phagocytic cells are stuffed with lymphoid cells still in a fair state of preservation. The large cells in the centres of the lymph nodules sometimes undergo necrosis, probably in consequence of lack of nutrition.

This brief statement of the proliferation and phagocytosis occurring in diphtheria is based on the histological study of 220 cases of diphtheria, of which a full report will be published shortly by Councilman, Pearce and myself.

Pratt has recently shown in a study of fifty cases of acute lobar pneumonia that the micrococcus lanceolatus causes marked proliferation of the cells lining the alveoli, the pleural cavities, and the lymphatics; these newly-formed cells are very phagocytic, incorporating and digesting polynuclear leucocytes, lymphoid and plasma cells, and red blood-globules. The proliferation is more marked in the early and in the late stages of the disease than in the middle stage, when the exudation of polynuclear leucocytes is abundant.

The acute lesions of the glomeruli of the kidney throw much light on the question of proliferation due to bacterial toxins. The organisms most frequently concerned are the micrococcus lanceolatus and the streptococcus pyogenes. The primary lesion from which the toxin escapes into the circulation is often an acute endocarditis; or the toxin may be secreted directly in the circulating blood in consequence of a septicæmia only. In other cases the primary lesion and the source of the toxin are more remote from the circulation. The lesions produced in the glomeruli vary from necrosis and exudation to pure proliferation.

The toxin secreted by the micrococcus lanceolatus causes proliferation almost exclusively of the endothelial cells lining the capillaries of the glomeruli. In one case of acute endocarditis, in which death occurred at the end of four weeks, the kidneys showed an essentially pure type of acute proliferative intracapillary glomerulo-nephritis. Mitotic figures in the endothelial cells were numerous; repeatedly two were found in one section of a single glomerulus.

With the streptococcus pyogenes the lesion produced in the glomeruli varies greatly; sometimes it is entirely exudative, at other times there is a marked proliferation of the capsular epithelium or of the capillary endothelium; proliferation and exudation are often combined in various proportions.

In one case of streptococcus endocarditis and septicæmia there was marked proliferation of the capsular epithelium and also in places of the epithelium at the beginning of the tubules; in one place two mitotic figures in the tubular epithelium were found side by side. Many mitoses were found in the capsular epithelium. In some of the capsular spaces there was a little fibrin and a few polynuclear leucocytes. Occasionally phagocytic cells were found within the capsular space; the inclusions consisted of polynuclear leucocytes and red blood-globules.

Certain organisms, such as the typhoid and tubercle bacilli, produce mild toxins which act slowly and usually produce proliferation only, but under certain conditions, especially when the organisms are massed together in large numbers, the toxins may be concentrated and produce necrosis and a purulent exudation.

In typhoid fever a mild diffusible toxin is formed which causes great proliferation of the endothelial cells lining the lymphatics, and the reticulum of the lymphoid tissue of the intestine and the mesenteric lymph nodes; it also causes proliferation of the endothelial cells lining the bloodvessels of the intestine, liver, and spleen All of these newly-formed cells are extremely phagocytic and incorporate lymphoid and plasma cells, polynuclear leucocytes, and red blood-corpuscles. Phagocytic cells formed within the bloodvessels are often carried by the circulation to the liver, where they give rise to miliary infarctions by blocking up the capillaries. In the spleen the phagocytic cells may occlude the blood sinuses, giving rise to necroses.

Occasionally, and almost invariably following an attack of typhoid

fever, the typhoid bacillus finds suitable conditions for abundant growth. Under these circumstances it produces a marked local reaction, namely, necrosis and purulent exudation like the more virulent organisms already mentioned.

The tubercle bacillus produces a variety of lesions. The typical lesion is, of course, the miliary tubercle, a clump of epithelioid cells produced by proliferation from endothelial and connective-tissue cells. In some situations, as in the lungs, epithelial cells may also take part in the proliferation. Giant cells may or may not be formed. Ordinarily these epithelioid cells show little evidence of phagocytosis, but in certain situations, such as in the meninges of the brain, and in the lymphatics of lymph nodes, there may occur a very extensive diffuse proliferation of the endothelial cells which distend the lymphatics widely and show marked phagocytic properties; so that an early diffuse tuberculosis of a bronchial lymph node may very closely resemble a mesenteric lymph node of the early, hyperplastic stage of typhoid fever.

On the other hand, in caseous pneumonia the exudation is often as marked as the proliferation, and in certain rare cases the tubercle bacillus acts like the pus organisms and produces a purulent exudation. In these cases the organisms are present in great numbers, and the toxin is probably much more concentrated than usual.

In the lesions thus far considered, proliferation of endothelial cells has played a very important part. It can be caused apparently by a great variety of toxins; several examples have been given. This proliferation always takes place by mitosis; careful search of fresh, well-preserved tissue has always shown enough typical mitotic figures to account for the newly-formed cells. In all of the situations in which the endothelium proliferates, except the glomeruli, the newly-formed cells are extremely phagocytic. They incorporate a certain definite group of cells, namely, polynuclear leucocytes, lymphoid and plasma cells, and red blood-globules; they never incorporate epithelial or other endothelial cells. The included cells seem normal at the time they are taken up; occasionally the lymphoid cells have been in mitosis. After inclusion for a time in the phagocytic cells they show more or less evidence of degeneration; the nucleus first stains intensely, then dissolves more or less irregularly, and finally disappears.

The kind of cells which a phagocyte incorporates depends on its

situation in the tissue; if it lies in lymphoid tissue it takes up lymphoid cells; if in a blood sinus of the spleen it encloses red blood-globules, often a dozen or more.

In acute proliferative intracapillary glomerulo-nephritis I have never been able to find any evidence of phagocytosis.

Phagocytic cells necessarily have the power of amœboid motion, otherwise they could not incorporate other cells. In one very perfectly preserved case, the first mentioned in this paper, the young endothelial cells formed by proliferation from the lining endothelium of the lymphatics were found actively emigrating from the vessels into the surrounding tissue.

Under certain circumstances bacterial toxins cause proliferation also of epithelial cells. This is shown most convincingly in cases of acute capsular glomerulo-nephritis; mitotic figures are easily demonstrable and are often comparatively numerous. Occasionally the more highly differentiated epithelial cells at the beginning of the renal tubules also show active proliferation. Rarely these new-formed cells in the capsular spaces contain inclusions, usually polynuclear leucocytes or red blood-globules. They would probably contain more inclusions if the proper cells were within reach. Proliferation of epithelium also takes place in pneumonia in the alveoli and in the pleural cavities; mitotic figures, as a rule, are readily found. The newly-formed epithelial cells are desquamated often in large numbers and seem as phagocytic as endothelial cells, which they resemble in every way. The best proof that epithelial cells are phagocytic is the fact that they often can be found containing cell inclusions while they still are attached to the walls of the alveoli.

It is to be noticed that the epithelial cells which have been demonstrated to proliferate and to become phagocytic under the action of bacterial toxins are all cells of a low, undifferentiated type; they are flat cells which resemble endothelial cells and probably perform much the same functions.

There are two situations in which I have found phagocytic cells where their origin is less easily determined.

In one end of the left kidney of a very young child who died of diphtheria complicated with focal pneumonia and suppuration of both middle ears, there were found several small grayish areas, the largest 4 mm. in diameter, running from the papillæ of the pyra-

mids into the cortex. The areas were rather soft, but not fluid; in places small hemorrhages had taken place into them. Unfortunately no cultures were made from these small areas, which microscopically showed an acute pyelonephritis. The tubules in the pyramids were dilated and filled chiefly with phagocytic cells; a few polynuclear leucocytes were present, but most of them were enclosed within the phagocytes. In the connective tissue between the tubules there were many phagocytic cells and some polynuclear leucocytes, lymphoid, and plasma cells. In the cortex the areas consisted almost entirely of phagocytic cells lying in the tubules and in the intertubular tissue. In some places all evidence of tubules had disappeared and there existed large areas of phagocytic cells, with here and there a few polynuclear leucocytes and lymphoid and plasma cells between them.

In the pyramids many of the phagocytic cells contained large numbers of bacilli, which in their morphology and staining reactions resembled in every respect the colon bacillus. The organisms also occurred to some extent outside of the cells; in the cortex they were much fewer in number and occurred mostly in clumps.

So far as could be determined from a study of the sections the phagocytic cells arose entirely in the intertubular tissue. Several of them were found immigrating into the tubules, having passed but part way through the basement membrane. They were also often present in numbers between the renal cells and the basement membrane, apparently having pushed the cells from the wall. In other instances they had distended the lumina of the tubules and flattened the epithelial cells.

The second case is more difficult. In the epididymis of an actively functioning testicle removed from a man, seventy-two years old, in consequence of hypertrophied prostate, there were found great numbers of perfectly formed spermatozoa and also numerous huge phagocytic cells incorporating and digesting the spermatozoa by the hundreds. These phagocytic cells cannot be polynuclear leucocytes, because the latter are never phagocytic for other cells. They can be only epithelial or endothelial cells; the latter view seems the more probable because it is difficult to conceive of the rather highly differentiated epithelial cells lining the epididymis being transformed into phagocytic cells.

The question whether bacterial toxins can cause connective-tissue

cells to proliferate and to become phagocytic is not easy to demonstrate. The best evidence is furnished, perhaps, by tuberculosis, but it is not conclusive. It is easy to show that a good deal of connective tissue reticulum is formed between the epithelioid cells in the periphery of a miliary tubercle and also outside of the tubercle; but that does not prove that the epithelioid cells have produced that reticulum, and therefore necessarily are connective tissue cells. Wherever lymphoid and plasma cells are collected in numbers a reticulum always forms between them. In the more chronic forms of capsular glomerulonephritis a connective-tissue reticulum extends in from the capsule and out from the glomerular tuft, and spreads gradually between the epithelial cells, in places forming a sort of basement membrane on which they tend to arrange themselves. In this way the capsular space is often divided into a number of small gland-like cavities. In neither of these two cases is it possible for the connective tissue reticulum to have been produced by the cells which lie in its meshes. The reticulum seems to grow in between the cells, because there is a physiological need of it.

It is not improbable that a good many of the phagocytic cells in the typhoid lesions of the intestine, especially in the muscular coat, are derived from the connective-tissue cells; but it is not easy to demonstrate it, partly because endothelial cells occur practically everywhere, partly because the connective-tissue cell away from the intracellular substance it produces possesses no very definite characteristics.

In connection with the subject of this paper the following case is of interest:

A woman, forty-eight years old, with alcoholic history, died of hypertrophic cirrhosis after symptoms lasting about seven months. The inner surface of the bladder, except at the neck, was found everywhere studded with slightly elevated, flattened, grayish to yellowish-gray nodules of a rather translucent appearance, varying in size from 1 mm. to 2 cm. in diameter. Only occasionally were the edges of the nodules overhanging. They projected from 1 to 4 mm. above the surface, and seemed to lie wholly within the mucous membrane, as they were freely movable over the underlying muscle tissue. Two or three of the nodules showed slight hemorrhages. So far as could be made out the nodules were not subdivided into papillæ—*i. e.*, they did not present a cauliflower appearance. The mucous membrane over the nodules was smooth and glistening.

The condition was diagnosticated as multiple papillomata of the bladder.

Microscopic examination of the nodules after the fixation of the tissue in

Zenker's fluid, three hours post-mortem, showed that they were due to collections of large phagocytic cells in the lymph spaces of the upper part of the submucosa. The cells were always most abundant just beneath the epithelium; in the smaller nodules they were confined to this situation, but in the larger nodules they extended more or less deeply into the submucosa, but never so far as to reach the underlying muscle tissue.

The capillaries and larger bloodvessels in the nodules were more or less congested, and the tissue around them showed marked infiltration with lymphoid and plasma cells. There were also numerous lymphoid and plasma cells beneath the mucous membrane and around the vessels between the nodules.

The epithelium of the mucous membrane was usually well preserved. Over the nodules it was much thinned, and in places was reduced to a single layer of cells, or was even missing.

The cells in the nodules varied a good deal in size, but usually were very large and round, polygonal or irregular in shape; the protoplasm, as a rule, was homogeneous and stained rather deeply with eosin. The nuclei, usually single, but sometimes two in number, were vascular in character, round, oval, or irregular in shape and usually eccentrically situated.

The inclusions in these large cells were of two sorts, bacteria and cells.

The bacteria were short rods, in general occurring in small, closely aggregated clumps which often lay within vacuoles. The number of organisms in a clump varied from half a dozen to dozens. Some cells contained as many as seven or eight clumps of organisms. Other cells contained from a few to hundreds of these organisms scattered diffusely in the protoplasm.

The bacteria were found almost entirely within the phagocytic cells; some of them stained sharply, others faintly; many were evidently dead and stained faintly or deeply with eosin. In the cells where the organisms seemed to be growing most rapidly they were usually shorter and plumper than in the cells which contained fewer of them. Occasionally short chains of two to four members were found. The Gram staining method gave negative results. It is impossible, of course, to say what the organism is. Morphologically and tinctorially it belongs to the colon group.

In places, especially within the larger nodules, nearly every phagocytic cell contained organisms. In other places they were not found in more than one cell in twenty. They were always more numerous near the surface of the nodules than in the deeper portions.

The cells included in the phagocytes were chiefly polynuclear leucocytes and lymphoid cells. Occasionally red blood-globules were incorporated. Most of the inclusions were so far digested that their nature could not be made out. The number of inclusions in a cell varied greatly, but rarely exceeded four or five, although occasionally there were over a dozen. As a rule, the inclusions lay within vacuoles. Within the protoplasm of many of the phagocytic cells were small hyaline bodies of varying size stained pink, and lying in vacuoles. Evidently they were the remains of incorporated cells. Many of them resembled closely the inclusions in the cells of carcinoma.

The nature of these phagocytic cells is difficult to determine absolutely. They resemble in all respects the phagocytic cells found in the lesions of typhoid fever. In all probability they are endothelial cells; but it is difficult to exclude entirely an origin from connective-tissue cells.

Where the phagocytic cells were numerous very little evidence of connective tissue could be found. At the bases of the nodules single phagocytic cells were present in the submucosa, lying apparently in spaces between the strands of fibrous tissue. The inclusions in this situation consisted chiefly of hyaline, often concentrically layered, refractive, spherical bodies. The cells often showed forms suggested of amœboid motion. They seemed to lie in lymph spaces.

Distinct lymphatic vessels were very few in number; they contained phagocytic, lymphoid, and plasma cells.

In the mucous membrane covering the nodules phagocytic cells were often found, sometimes in considerable numbers, between the epithelial cells. They probably had migrated to that situation from the underlying tissue.

Occasionally in some of the nodules there were small collections of leucocytes, attracted, so far as could be made out, by degeneration of phagocytic cells.

It seems reasonable to conclude that these tumor-like nodules, composed of phagocytic cells lying in the submucous tissue of the bladder, are due to the action of the organisms found in such large numbers within many of the cells. Certainly, the nodules have none of the characteristics of a true tumor-formation.

So far I have considered the action of toxins on only three forms of cells. Their action on three other forms I will mention briefly.

The great increase in the number of the polynuclear leucocytes in the blood in infection with certain bacteria, especially the pus organisms, is well known. The leucocytosis produced is of diagnostic importance; so also is the increase in the number of eosinophiles in trichinosis.

Of greater significance in this connection is the increase of lymphoid and plasma cells which takes place in certain cases of scarlet fever and diphtheria. This has been considered at length by Councilman in his paper on "Acute Interstitial Nephritis." The cells collect in the veins of the pyramids in the kidney; they emigrate from the vessels into the intertubular tissue, and continue to proliferate there; by their numbers they interfere with the function of the kidney, and may cause destruction of the tubules. The process in some respects closely resembles a malignant growth, such as leukæmia or lymphosarcoma.

The tendency of the cells which proliferate under the action of toxins is to degenerate and disappear as soon as the agent to which they owe their existence is destroyed or is neutralized. The best example is afforded, perhaps, by the resolution which takes place in the hyperplastic patches of Peyer and in the mesenteric lymph nodes in typhoid fever. The affected tissues quickly recover their normal appearance. In certain situations the results of the proliferation are more permanent and more disastrous. For example, the renal glomeruli may be destroyed partially or entirely by occlusion of the capillaries, or by the formation of fibrous tissue in the capsular spaces, and be converted into small, contracted masses of hyaline connective tissue.

The processes of proliferation and phagocytosis which I have been describing as due directly to the action of toxins are regarded generally as reparative in nature. Similar processes certainly occur in repair. Is it possible to differentiate them?

In repair, cells proliferate for definite purposes; epithelium to cover denuded surfaces; connective tissue and lymph endothelial cells to replace losses of tissue and to remove foreign bodies, such as necrotic cells, fibrin, fat, myelin, etc.; blood endothelium to form new blood-vessels for the nourishment of the new tissue.

The cells, however, which proliferate under the direct action of toxins, multiply greatly in excess of need, and show a lack of definite purpose; they may exert some more or less beneficent action such as possibly the production of antitoxins, but they can no more be regarded as reparative than the exudation called out by the toxins; both may work infinite harm.

As we have seen in the cases cited, phagocytic cells may block up lymphatics and undergo necrosis; they may be carried to the liver as emboli, blocking up the capillaries and giving rise to focal necroses of liver cells; they may enclose and destroy the lymphoid cells in lymph nodules, and then undergo necrosis themselves; they may occlude the veins in the spleen, giving rise to infarctions; they may occlude the capillaries of the glomeruli by growth within the vessels or by pressure from without; they may give rise to tumor-like formations. Lymphoid and plasma cells may multiply in the circulation, and may invade and multiply in the kidney, interfering with its functions and causing its destruction. The phagocytic cells are phagocytic beyond

all bounds of necessity, and destroy great numbers of active, useful cells.

These are all abnormal, and to a certain degree malignant properties.

DISCUSSION.

DR. WELCH: I have been greatly interested in Dr. Mallory's paper. His observations relate to questions of fundamental importance in pathological cytology, and are based upon long and careful studies. Of especial interest are Dr. Mallory's views concerning the powers of toxins, especially when of feeble potency, to stimulate cells directly by proliferation. He is, of course, familiar with the attacks made upon this doctrine by Weigert and his pupils. As, according to Weigert, the necessary primary damage inflicted by so-called external stimuli upon cells may be of a subtle and not readily demonstrable character, it becomes a matter of great difficulty to exclude positively the intervention of such lesions between the action of a toxin and the proliferation of cells. But even if this be admitted, we must agree with Dr. Mallory that so far as our present methods of observation go, it appears that cells may be incited by external agents directly to growth and multiplication. The observations of Professor Loeb upon the influence of chemical substances, apart from spermatozoa, in stimulating ova to segmentation speak also in favor of Dr. Mallory's conclusions.

The interpretation of endothelial and other large cells containing leucocytes is not always easy. The large cell may be devouring the leucocytes, as described by Dr. Mallory, but sometimes the leucocytes are attacking and destroying the large cells, and while the fate of one or the other type of cell may be decisive as to the nature of the combat, I have sometimes found difficulty in deciding which of the cells is to be regarded as the phagocyte.

THE PATHOLOGY OF ACID INTOXICATIONS.

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The object of this report is to give the results of observations made to determine what are some of the conditions of disease in which organic acids are present in pathological quantities in the urine and, therefore, in the blood; and, further, to discuss certain points connected with the toxic effects of acids. It is now well established that in the case of diabetes there is often an organic acid in the blood in pathological amounts, and it was thought desirable to ascertain whether this might not be so in other states.

The inquiry itself was suggested by the fact that organic acids are normally present in the body, and that it is easy to conceive of derangements arising either from (*a*) increased formation of acids, (*b*) diminished combustion of acids, or (*c*) both together. There is also the possibility that organic acids may be formed which are wholly foreign to the organism under normal conditions.

The method of inquiry was suggested by the fact that free acids do not occur in freshly excreted urine except, perhaps, in the merest traces. Acids entering the blood are rapidly neutralized by basic elements and only the salts of the acids pass into the urine. In other words, all the acid radicals in the urine, whether these be normal or pathological, are there in union with basic bodies.

In health the urine contains four chief acids united to five different bases. Three of the acids are inorganic acids—namely, HCl, H_2SO_4, H_3PO_4; one of them is organic—uric. The five bases are Na, K, Ca, Mg, and NH_3.

If we determine the acid radicals of the acids mentioned and express their acid values in terms of sodium, we find that these acid values very nearly neutralize the basic values of the five bases, expressed

likewise in terms of sodium. In other words, these acids and bases of the normal urine neutralize one another very nearly.

I say *very nearly*, because the acids almost always show a moderate apparent excess. The excess of acid amounts from 5 to 10 per cent. of the total acids. This excess of acid is independent of the acid reaction of the urine. The acid reaction depends on the presence of acid salts, and these are taken into account in calculating the balance of acids and bases. But as the acids and bases of the normal urine neutralize one another in the sense that there are no free acids or bases, it is clear that some unknown organic base is present, united with the apparent excess in acids. What this base is we do not know. It has been suggested that it is creatinine.

We know only that the five inorganic bases of the urine do not suffice to neutralize the acid radicals. It should thus be evident that the excess in bases is *apparent* and not actual.

On considering these facts it becomes clear that if the urine should contain organic acids other than uric in considerable amount they would make themselves evident in balancing the acids and bases by an *apparent excess in bases.* An experimental example will show this clearly.

A dog weighing 50 pounds was given large doses of lactic acid (55 gms. per day); part of this was burned in the body, the greater part was eliminated in the urine in basic union. The usual bases are therefore apparently in excess of the usual acids, thus in forty-eight hours' urine: bases, 34.56 gm.; acids, 9.74 gm.; apparent excess of bases, 24.87 gm. (in terms of sodium). One hundred and ten gms. of lactic acid correspond to 30.018 gms. of sodium—*i. e.*, the result represents nearly 100 gms. of lactic acid in urine. In other words, an apparent excess of bases points positively to the presence of an acid which is neither HCl, nor H_2SO_4, nor H_3PO_4, nor uric acid—*i. e.*, it is an *organic* acid of known nature in this case.

This method of detecting the presence of an organic acid enables us to form an approximate estimate of the quantity of the unknown acid. It gives no clue to the nature of the acid. It is helpful, however, in telling us how much of any suspected acid we have to account for.

This method was employed by us in the study of various clinical conditions, viz.:

1. Cases of dilatation of the stomach with delayed emptying.
2. Cases of the classes known as arthritis deformans and rheumatoid arthritis.
3. Cases of cirrhosis of the liver.
4. Cases of acute gastritis.
5. Cases of diabetes.

The following experimental conditions were also studied:

a. Phosphorus and arsenical poisoning.
b. Phlorhizia poisoning.
c. Starvation.
d. Anæmia from bleeding.
e. Administrations of mineral and organic acids.

The results obtained in different clinical and experimental states will be discussed before the significance of the results is considered.

Six cases of dilatation of the stomach with atony and seven cases of arthritis deformans, or rheumatoid arthritis, were studied. In each instance the bases were found to be in excess of the acids. Sometimes the excess is very small, sometimes it amounts to 0.7 gm. of sodium in twenty-four hours. The excess of bases, indicating the presence of an organic acid, was never very large in any of these patients, but was a constant feature. An example of the excess of bases is the following:

Patient with arthritis deformans of seven years' duration. Twenty-four-hours' urine contained:

K_2O . .	= 1.3370	SO_3 (preformed) .	= 0.9961
Na_2O .	= 3.9780	SO_3 (combined) .	= 0.0388
CaO . .	= 0.1345	P_2O_5 (bibasic) .	= 0.6725
MgO .	= 0.1861	P_2O_5 (monobasic .	= 0.1400
N (NH_3) .	= 0.9663	Cl . . .	= 3.8830
		Uric acid . .	= 0.0868
Total bases	= 6.6019 gms.	Total acids .	= 5.7747

Excess of bases = 0.7747 gm. sodium.

The nature of the organic acid discovered to be present in these cases is at present unknown, but is being made the subject of special investigation.

In regard to cirrhosis of the liver it was found that while an excess of bases sometimes is found in these cases it is by no means an essen-

tial accompaniment of the disease. It is in cases of diabetes that the largest excess of bases has been observed. An excess is apparently a regular feature of diabetes, but the preponderance of bases is greatest where the clinical conditions are the least favorable. In coma or just before coma the excess in bases is always very large. An example of the large excess in bases is seen in the following figures, which are from a patient with diabetes two weeks before the onset of coma. The twenty-four-hours' urine contained:

K_2O . .	= 2.0630	SO_3 (preformed) .	= 0.6918
Na_2O .	= 3.1460	SO_3 (combined) .	= 0.0743
CaO . .	= 0.7364	P_2O_5 (bibasic) .	= 0.7932
MgO .	= 0.1295	P_2O_5 (monobasic) .	= 0.1759
NH_3 .	= 2.8930	Uric acid . .	= 0.0182
		Cl . . .	= 1.9652
Total bases = 8.9679 gm.		Total acids .	= 3.7184
Bases in excess = 5.2495.			

In reference to poisoning by phosphorus, arsenic, and phloridzin, it was found that there is no necessary excess in the bases of the urine in these conditions. In starvation and after bleeding the normal relation of acids and bases in the urine was observed. The administration of mineral and organic acids was regularly followed, as might be expected, by an increase in the excretion of bases.

THE REMOVAL OF ALKALI FROM THE BODY BY ACIDS. One of the most important effects of introducing an acid into the organism relates to the alkali materials of the body and the alkalescence of the blood. If we introduce an acid into the body, either by way of the digestive tube or by direct infusion of a weak solution into the blood in a quantity consistent with the continuance of life, this acid acts at once on the alkali present in the blood and in the cells which the blood nourishes. A prompt neutralization of the acid occurs which involves the appropriation of basic elements. The most important of these elements is the sodium of the sodium carbonate and sodium phosphate, which are the chief factors in maintaining the alkalescence of the blood. This supply of alkaline reacting alkali (or native alkali) has been estimated as equivalent to 180 mg. NaOH in 100 gms. of blood. The values are lower for the plasma, and probably still lower for the cells of the body generally. If we estimate this total "native

alkali" of the entire body at 125 mgs. NaOH for each 100 gms. (and this is a maximum estimate) we find that a body weighing 50 kg. would possess an alkali value equivalent to 62 gm. NaOH.

It is easy to see that this relatively small quantity of alkali would be quickly exhausted by a persistent acid intoxication involving even the formation of small amounts of acids. Thus in one of the cases of rheumatoid arthritis that has been recorded the quantity of unknown acid in the urine is frequently equal to 0.5 gms. NaOH per day. In a case of diabetes like the one referred to the quantity of alkali required to neutralize the acid would completely exhaust the native alkali of the body in less than two weeks, if such a thing were conceivable as consistent with life. But as patients live for months with such a large excretion of organic acid, it is evident that there must be other sources of alkali for the neutralization of pathological acids. One naturally thinks of the fixed alkali of the tissues—that is to say, the calcium and phosphate of the bones. But a very simple calculation shows that the supply of this fixed alkali would suffice to neutralize only a small amount of acid. There must therefore be another and more permanent source of alkali. This is known to exist in the ammonia which is constantly being formed as the result of the decomposition of proteid material.

The excretion of NH_3 which is available for the neutralization of acid is derived from two distinct sources: one of these is the proteid metabolism of the active cells of the body generally; the other is the decomposition of proteid food.

The NH_3 derived from the general proteid metabolism represents the chief normal nitrogenous product of cell activity. In conditions of health this NH_3 unites with CO_2 of the blood to form ammonium carbonate. Recent experiments show that in the liver a very active conversion of NH_3 into urea takes place, and there is no doubt that the liver is to be regarded as the chief but not exclusive seat of urea formation. The NH_3 derived from the intestinal contents appears not to be split off from the proteid food in the gut as the result of putrefaction, but is thought to be split off by the epithelial cells during the absorption of peptones. Whatever may be the seat of origin of this NH_3, it is clear that considerable NH_3 comes from proteid food, for on a meat diet the blood of the mesenteric veins contains a higher percentage of ammonia than the blood of other parts of the body.

This elementary NH_3 is converted into urea on reaching the liver. I shall presently mention the evidence which appears to me to indicate that this alimentary ammonia may be utilized, like the metabolic ammonia, to neutralize acids.

In a state of health the NH_3 derived from both these sources is in very large part utilized by the formation of urea. Hence, in the urine we find that the N of NH_3 is equal to only about 1 to 5 per cent. of the total N of the urine. The absolute amount of NH_3 in the urine does not amount to more than 0.5 to 1.5 gm. in twenty-four hours in an adult person.

One would naturally infer that if a portion of the NH_3 which normally goes to the formation of urea should be diverted for the utilization of an organic or other acid the urine would contain an excessive amount of NH_3. This is in fact the case. Clinically the largest excesses of NH_3 in the urine are observed in diabetes and in cases of phosphorus-poisoning.

In diabetes the daily quantity of NH_3 excreted sometimes amounts to 8 or 10 gms., a really enormous output. If we estimate the quantity of NH_3 normally excreted at 1 gm. per day this leaves from 7 to 9 gms. available for neutralization of acid. In the case of diabetic coma the organic acid is chiefly β-oxybutyric acid, and 7 gms. of NH_3 will neutralize about 50 gms. of β-oxybutyric acid.

The percentage of N of NH_3 often reaches very high figures. Thus in phosphorus poisoning it has been known to amount to over 30 per cent. of the total N. In one of our cases of diabetes the NH_3 amounts to 20 per cent. of the total N. In the case of one dog fed on lactic acid the N of NH_3 reached 32 per cent. on one occasion. These are, of course, exceptionally high figures.

In the slighter grades of poisoning by acids it is not always easy to say whether we have or have not an excess of N of NH_3 in the urine. This is because it is often difficult to determine how much N of NH_3 a patient should normally have in the urine on a given diet. We are justified in concluding, from an examination of the results in many cases of slight acid intoxication, that neither the percentage nor absolute amount of N of NH_3 gives us a reliable index of the quantity of pathological organic acids in the urine. A good example of this is seen in our second case of dilatation of the stomach. On November 9, 1899, this patient's urine showed only 0.1521 gm. of NH_3 in

twenty-four hours, a percentage of 0.33. This amount of NH_3 is well within the limits of the normal, and it is far short of the quantity required to neutralize the excess of bases present—namely, 1.65 gms. for the twenty-four hours.

On the other hand, we have sometimes met with cases where the N of NH_3 was above the usual in percentage, but in which the relation between acids and bases was normal. The explanation of such findings is not yet clear, but the presumption is that this N of NH_3 comes from proteid food.

There is still another point to be noted about the rise of the N of NH_3 as an index of the degree of intoxication. There appears to be a limit to the proportion of the total NH_3 formed in the body which can be utilized for the neutralization of acid. We do not know of any reliable records which show more than 30 to 40 per cent. of N of NH_3 in the urine as the result of acid poisoning. The important thing to observe is that when the NH_3 reaches a high percentage, but still fails to neutralize the acid, the other alkali reserves of the body are called into use. First in importance is the alkaline sodium of the plasma. The sodium carbonate is decomposed by the acid, with liberation of CO_2, which doubtless finds a ready escape through the lungs. The basic element is thus robbed from the blood for the neutralization of acid. If the demand for the sodium carbonate of the blood is large there is soon a reduction in the alkalescence of the blood that is incompatible with the maintenance of life. Potassium may be similarly withdrawn.

Thus it seems evident that while under some circumstances the amount of NH_3 in the urine is a reliable index to the quantity of acid that is daily being excreted there are important exceptions to this rule. From what has been already said it can be inferred that the balancing of acids and bases in the manner employed by us in studying our cases of dilatation of the stomach, etc., is the only satisfactory way we possess of estimating the daily output of acid, and is greatly to be preferred to the simple determination of the NH_3 of the urine. Similarly in many cases of diabetes the NH_3 content of the urine taken by itself would cause us to underestimate, often considerably, the quantity of acid excreted. Here, again, the balancing of the acids and bases enables us to determine, probably with great accuracy, the amount of acid that is being eliminated.

EXCRETION OF CALCIUM AND MAGNESIUM IN INTOXICATION BY ACIDS. Ammonium and the alkali metals, especially sodium, have been referred to as serving the important purpose of removing acid from the organism after effecting its neutralization. There is good evidence that under some conditions the alkali earth metals (calcium and magnesium) are called upon to perform a similar protective function. It is unlikely that the acid acts directly on the fixed alkali of the bones, which are the main seat of the calcium and magnesium of the body. Probably the acid acts on the small amount of calcium and magnesium compounds in the blood, and the fixed alkali of the bones is then taxed to replace the bases taken from the blood, in order to maintain an approximately normal percentage of these important elements.

The recent studies of Gerhardt and Schlesinger leave no doubt that the increased output of calcium, which has for some time been recognized as occurring in diabetes, is the result of the acid intoxication which exists in this disease. This is clearly indicated by the fact that the internal use of sodium bicarbonate for the protection of the calcium of the body is followed by a distinct reduction in the calcium output. In one of Gerhardt's and Schlesinger's patients the CaO amounted to 1.182 gms. in twenty-four hours—a quantity many times in excess of the normal. In this patient the ammonia was 6.78 gms. during the corresponding period.

In one of our diabetic patients the CaO equalled 0.98 gm.—a distinctly excessive amount. During the same twenty-four hours the patient excreted 1.89 gms. of NH_3, and the N of the NH_3 reached 20 per cent.

In a dog which Dr. Baldwin was studying in our laboratory, and which was taking 60 gms. of commercial lactic acid per day, there appeared to be a distinct increase both in calcium and magnesium in the urine. The N of NH_3 was 32 per cent. in this case, the bases were 34.56 gms., while the acids were only 9.74 gms., showing the removal of an amount of acid equivalent to 24.8 gms. of sodium. Thus it is likely that lactic acid is capable of removing calcium as effectively as is β-oxybutyric acid.

There is no reason to doubt that the persistent withdrawal of excessive amounts of calcium from the body leads in time to a deprivation of the bones in calcium salts. I do not know whether such a condition has been demonstrated in diabetes, but think its occurrence might

safely be predicted. The magnesium of the organism appears to suffer absolutely less than the calcium, but whether it suffers relatively less is not clear.

Enough has now been said to illustrate the fact that an immediate and important consequence of the introduction of acids into the organism is a withdrawal of alkali from the body which is proportionate to the amount of acid requiring neutralization. The chief alkali concerned with this elimination of acid is ammonia; but under some circumstances the sodium of the blood and the calcium of the bones may also be significant. The constant formation of ammonia by the tissues enables the organism to remove a large amount of acid daily, during a long period, without damaging the organism in any way that is apparent. Organisms which are unable to offer large amounts of NH_3 (owing to herbivorous habits) succumb to relatively small amounts of acid. This is the case with rabbits. When the sodium of the blood is regularly called into requisition a grave danger threatens the subject of an acid intoxication—namely, the danger attending a considerable reduction in the alkalescence of the blood. Especial reference will elsewhere be made to this effect in the blood.

Effect of Administering Alkali on the Excretion of NH_3 and Ca. It is a fact of much physiological interest and of considerable practical importance that the administration of alkali is capable of greatly modifying the ammonium excretion of the organism. It is probably true that in any condition attended by an excessive output of NH_3 the use of alkaline salts of sodium or potassium is followed by a reduction in the output of ammonia. The explanation of that phenomenon is simple. If we give sodium carbonate by the mouth the salt is absorbed and serves to neutralize the excess of acid that is being accumulated in the organism. Carbonic acid, being diffusible, finds a ready escape by the lungs on being replaced by the pathological acid. The sodium salt of this acid is formed and there is no longer the same occasion for the diversion of ammonia. Thus the ammonia which would ordinarily be employed in the neutralization of the acid is converted, as in health, into urea.

The condition in which the effect of alkali administration has been most carefully studied is diabetes. There are numerous observations in which a reduction of ammonia has followed large doses of sodium bicarbonate or carbonate.

The influence of alkali given by the mouth is not limited to the replacement of ammonia. Recent observations on the output of calcium and magnesium in diabetes show very clearly that the excessive calcium loss is immediately checked by the use of considerable doses of sodium carbonate.

The fact that alkalies introduced into the organism are capable of replacing or supplementing the alkali resources of the body has been made the basis of therapeutic measures. It has been shown that rabbits poisoned by doses of acid that would ordinarily prove fatal quickly recover when treated with suitable doses of alkaline salts. In man the only observations relate to diabetic coma. It is essential to understand that here we have conditions very different from any which we can induce by experimental means through the use of acids. Any acid introduced for experimental purposes into an animal in an amount compatible with the maintenance of life can be promptly neutralized in large measure by the use of alkalies, but in diabetic coma the intoxicating acid, β-oxybutyric acid, continues to be formed in considerable amounts as long as the patient lives. Hence, we no sooner introduce the quantity of alkali necessary to bring the alkalescence of the blood back to its normal grade than this alkalescence begins to fall again in consequence of the continued production of acid. It is thus not surprising that in the majority of cases of diabetic coma the treatment by alkalies has failed. In a few cases, however, reported by Minkowski, Naunyn, Zinn, and Magnus-Levy, life has been prolonged. There are altogether six recorded cases of diabetic coma in which the free use of alkali by infusion and by the stomach has been followed by at least temporary recovery from the coma. It is, of course, desirable to realize clearly that any therapeutic measures based on the ability to neutralize acid by means of alkali must be regarded merely as temporary expedients. This is not true merely of diabetes, but of all states in which the organism is overloaded with an organic acid. Any rational therapeutics designed to give permanent results must contemplate either the diminished formation of the acid or acids concerned with the intoxication, or an increased combustion of the acid, or both results together.

It is not quite clear how good can be accomplished by the alkali treatment of all acid intoxications. It is, of course, of great importance to restore the alkalescence of the blood whenever this is

markedly reduced as in diabetic coma. We can do this by replacing the lost sodium of the blood by means of a sodium salt such as sodium bicarbonate. We can probably also replace the lost calcium of the body in an indirect way—namely, by preventing further calcium losses and by preventing the diversion of calcium taken with the food. But supposing these ends have been accomplished, the question arises, Is there any object in reducing an excessive output of NH_3, when this is present, by means of sodium salts? It is by no means clear that an increased output of NH_3, due to acid, is evidence of even a slight reduction in the alkalescence of the blood. The administration of sodium salts would, perhaps, have the advantage of postponing threatened coma. There are, however, instances like those we have mentioned, of a slighter clinical disturbance, attended with the excretion of unknown organic acids, such cases, for example, as those of arthritis deformans. Here there is no question of coma. In the few instances in which alkali has been used by us no improvement has been noted in the clinical conditions, and it certainly appears an open question whether we can expect to gain anything by reducing a possible slight excess in NH_3 output by means of alkalies. In these cases of *acidosis* (as we may call the slight grades of acid intoxication) there is probably an abundant supply of NH_3 for the neutralization of the acid, and it is still uncertain whether there is any advantage in replacing this base by one of our own choosing.

THE ACIDS CONCERNED IN ACID INTOXICATION AND THE ACTION OF INDIVIDUAL ACIDS. The nature of the acids concerned in cases of acid intoxication, including the slighter cases which we may call *acidosis*, is of the greatest interest, and the character of these acids may be expected to give us a clue to their origin in the organism. One cannot evade the conviction that such knowledge must precede any truly rational efforts to modify such intoxications as those under consideration. At the present time we know almost nothing of the chemical characters or origins of the acids concerned, excepting the recently acquired information relative to β-oxybutyric acid. We can review very briefly what little there is to say of the individual acids which may be looked upon with suspicion as agents in producing intoxication.

Volatile Fatty Acids. These are the monobasic acids, formic, acetic, propionic, butyric, and valerianic. These acids have been found in

small amounts in the urine in various pathological conditions, but only in small quantities. It is well known that the volatile fatty acids are greatly increased during the alkaline decomposition of the urine; it is less well known that urine free from such acids when fresh may soon develop them without becoming alkaline in reaction. This fact leads me to look with suspicion on much of the work that has been done on the fatty acids in the urine. Although some of this work may be reliable it is not easy to say which this is. We have had to throw out what seemed interesting results on the fatty acids in the urine from a patient with dilatation of the stomach, and in whom fatty acids were abundant in the gastric contents. In one case in our series of arthritis deformans patients the fatty acids were much less in amount than would account for the excess of bases. This was also the case in a patient with dilatation of the stomach and pyloric stenosis.

It is certain that the volatile fatty acids deserve to be newly studied in urine so fresh as to exclude the possibility of acid formation either outside the body or in the bladder. The increase in these acids found in fever, in leukæmia and in hepatic disease should be especially studied.

One is perhaps tempted to imagine that excessive carbohydrate fermentation in the stomach in cases of dilatation would be followed by the absorption and excretion of fatty acids. It must be remembered, however, that the lower acids of the hydrocarbon series are readily oxidized and that we have no good or proven grounds for expecting them to pass into the urine unless they are formed in considerable amount.

We have made some experiments in feeding animals with certain fatty acids which are not without interest. The injection of acetic acid directly into the blood in a dog was followed by the appearance of acetates and of an apparent excess of bases in the urine. A pig which was fed very large doses of acetic acid during many months grew very fat, and at autopsy showed an abundance of fat with a lower melting-point than the normal pig's fat. Acetates and formates appeared in the urine, but not in large amount, and very little acetic acid found its way into the feces. As the animal took an amount of acid equivalent to 50–100 grammes glacial acetic acid daily, there is no reason to doubt that the organism oxidized the greater part of the

acetic acid, much as it oxidizes alcohol. We have also fed two dogs on butyric acid, but have not yet finished the observations. Butyric acid is apparently a greater irritant to the gastro-enteric tract than acetic acid and induces diarrhœa readily.

It is probably fair to infer that the lower fatty acids, when absorbed from the digestive tract, are largely burned in the organism and are not largely concerned in producing states of acidosis or acid intoxication.

Lactic Acid. The relation of lactic acid to acid intoxication is a matter of much interest, since lactic acid is known to be produced in the organism in health, and has been held responsible by theorizers for many different states of disease. Two kinds of lactic acid are well recognized: first, the fermentative lactic acid, which is optically inactive and crystallizes with 18.18 per cent. H_2O; and, second, the sarcolactic acid, which rotates to the right and crystallizes with 12.9 per cent. H_2O. The inactive acid is considered to result from a union of the levorotary and the dextrorotary acid. Both acids are formed in normal conditions. Fermentative lactic acid is produced from carbohydrates in the course of digestion. Sarcolactic acid is produced probably by the liver and muscle, but whether from proteid or not is still unsettled. The occurrence of sarcolactic acid in the blood in health has been doubted, but the recent experiments of Morishema appear to leave no room for questioning the constant presence of lactic acid in the blood, in the liver, in the kidneys and in the intestinal walls. The acid thus formed must be burned in the body, for it does not find its way into the urine.

It is reasonable to suppose that there may be conditions of disease in which sarcolactic acid is either formed in excess or imperfectly burned. We know so little at present of the physiological conditions attending the formation and consumption of lactic acid that speculation as to the processes in disease are useless. We *do* know the following facts:

First. The removal of the liver in ducks and geese is followed by the appearance of an abundance of sarcolactic acid in the urine, united to ammonia. This was shown by Minkowski and points to impaired combustion of lactic acid due to failure in hepatic function. Second. Phosphorus-poisoning in dogs and in man is often followed by the appearance of lactic acid in the urine united to ammonia. It is be-

lieved that in phosphorus-poisoning we have an acid intoxication from lactic acid. The careful work of Münzer, who studied a series of suicidal cases in discouraged Austrian prostitutes, shows that lactic acid cannot always be found in the urine of phosphorus-poisoning. In one of our dogs the urine contained no excess of ammonia, and no lactic acid could be found, although leucin was abundant and the dog lived several days after the administration of the first dose of phosphorus. The subject seems to call for further study. Third. Morishema found a moderate increase in lactic acid in the blood after arsenical poisoning; but more work needs to be done before we can entertain the view that a lactic-acid intoxication is a feature of arsenical poisoning.

In one of our arthritic cases with an excess of bases no lactic acid could be found.

One feels on reviewing the subject that there is still considerable to be done in the study of the possible relation of lactic acid to disease. Minkowski's liver extirpations suggest that the increase of ammonia noted in cirrhosis of the liver should be considered in connection with sarcolactic acid. At present the one important pathological fact in human cases is that sarcolactic acid is sometimes found in phosphorus-poisoning.

As regards the possible relations of the second variety of lactic acid—the optically inactive acid—we are quite in the dark. This acid is formed in considerable quantities in cases of dilatation of the stomach, as the result of fermentation of carbohydrates. It is conceivable that the acid thus formed is only partly burned and that a portion of it is neutralized by bases and excreted by the urine as a lactate. We have as yet no results on this point from our cases of dilatation of the stomach, but the possibility suggested is worthy of investigation.

Experiments made by Dr. Baldwin show that very large quantities of lactic acid can be taken daily for a long time by a healthy dog. In one case more than 50 grammes of the commercial acid was taken for several weeks. A considerable quantity of the acid was burned in the body, but most of it was presumably carried into the urine, for the ammonia output was much increased.

It deserves to be noted that lactic acid appears to be much less toxic than propionic acid, of which it is the hydroxy acid. The

change in toxic properties effected by hydroxylation will be again referred to in connection with β-oxybutyric acid.

β-oxybutyric Acid. This hydroxy acid has the distinction of being clearly responsible for an important clinical condition—diabetic coma. It is a matter of some interest as illustrating the entry of scientific methods into medicine that Stadelmann, in 1883, succeeded in balancing the acids and bases in the urine in cases of diabetes and in correctly predicting from his results that the urine must contain some organic acid in large amount. He further separated an acid which he considered the cause of the apparent excess in bases. This was crotonic acid, but Minkowski soon after showed that the crotonic acid was derived from the decomposition of β-oxybutyric acid, and that it is the latter which we meet in the urine of diabetes.

The important paper of Magnus-Levy, published last summer, makes it likely that in all severe cases of diabetes the urine contains β-oxybutyric acid. Aside from states of coma the quantity is rarely more than 20 to 30 grammes in twenty-four hours. In the state of coma this acid is always present in very large amount. In one case the amount was 160 grammes in twenty-four hours under the influence of alkali, which facilitates its removal.

An estimate of the alkali in the adult human body indicates that the amount in the blood and tissues is only enough to neutralize about 80 grammes of β-oxybutyric acid. It is the ammonia of the tissues which enables the organism to get rid of the acid that is constantly formed.

Of the origin of the acid we are still somewhat in the dark. It is commonly taught that it comes from the metabolism of proteid. The calculations of Magnus-Levy show, however, that the amount of proteid decomposed is not sufficient to account for the enormous amounts of acid found. It must, therefore, come in part from the fat tissues or fatty food on which the diabetic so largely lives.

The results of experiments made with β-oxybutyric acid indicate that its action in producing coma depends on no specific toxic properties, but rather on its action in removing alkali from the blood and so reducing the alkalescence of the blood. It is interesting to note that β-oxybutyric acid is much less toxic to dogs and other animals than butyric acid. The hydroxylation has an effect similar to that observed in the case of lactic acid, which is less toxic than propionic acid.

β-oxybutyric acid has been found in small amounts in a variety of pathological conditions—in scorbutus, in some of the infectious diseases of childhood, in the coma of cancer, and in some disturbances of the intestinal tract. The conditions in which β-oxybutyric acid is found in small quantities are worthy of much closer study than has hitherto been given them.

Diacetic Acid. Diacetic or aceto-acetic acid has been regarded by Jaksch, Münzer and other writers as the cause of diabetic coma. There is no doubt that this acid is present in most, if not all, cases of diabetic coma, but even in the cases in which it is most abundant it is present in small quantity as compared with β-oxybutyric acid. There can be no reasonable doubt that diacetic acid contributes to the acid intoxication of diabetes, but, on the other hand, this acid must be regarded as a factor of minor importance in the production of coma.

Oxalic Acid—Uric Acid. These organic acids are frequently spoken of as contributing to intoxications, but without sufficient cause. Even when these acids are present in the largest amounts ever found in the urine, their quantity, individually and collectively, is so small that they can play no important part in affecting the excess of bases noted in a state of acidosis. These acids may, therefore, be dismissed as having no close relation to the subject under consideration.

When we come to the consideration of the aromatic acids we find ourselves again in the dark. It is known that benzoic acid pairs with glycocol or amido-acetic acid, probably in the liver and kidney, to be excreted as hippuric acid. There is thus a certain resemblance between the provision made for the removal of this aromatic acid and that which exists for the removal of acids of the fatty acid series and the mineral acids. But we do not know anything at the present time about the aromatic acids in their relation to acid intoxication in the human subject.

As to the nature of the organic acids of whose presence we have evidence in our cases of dilatation of the stomach, arthritis deformans and cirrhosis of the liver, there is simply nothing to be said at the present time. The process of isolating the acids concerned is likely to be long and difficult, but the task of recognizing these bodies deserves to be undertaken, since it holds out a hope of reaching a better understanding of a variety of pathological conditions.

In the preceding remarks frequent reference has been made to the influence of acids in reducing the alkalescence of the blood, and there is no doubt that the grave symptoms of acid intoxication observed in diabetes are due to the removal of alkali from the blood. If we inject a free acid into the blood of a rabbit or dog, death occurs before there is a complete abolition of the alkaline reaction of the blood. A considerable permanent reduction in the blood alkalescence appears incompatible with the maintenance of life in mammals. The reason for this is evident when we consider, even superficially, the conditions underlying the processes of respiration. The venous blood in the dog contains from 39 to 48 percentage volumes of CO_2, the arterial blood about 8 per cent. less. This considerable volume of CO_2 is held in the blood, not in a state of simple solution, but in combination mainly with sodium. The blood contains about 4 per cent. of sodium, but the greater part of this exists as sodium chloride, and a smaller part as sodium phosphate. Enough remains, however, to hold the large volume of carbon dioxide as a carbonate. When an organic or mineral acid enters the blood it displaces the diffusible carbon dioxide and appropriates the sodium, which is promptly carried out of the organism by means of the kidneys. It is easy to see that if the amount of sodium is much reduced the carbon dioxide liberated in the cells can no longer make its way to the lungs to find an exit from the body. In other words, there is an accumulation of carbon dioxide in the fluids and cells of the body which interferes with the oxidations essential to life, and occasions coma and death. Whether the presence of neutralized organic acid in the blood ever finds other expression in the symptoms of disease is a question which cannot be profitably discussed at present; but there is no reason to doubt that states of acidosis, like those we have described, as well as the graver intoxications, are essential features of some processes of disease.

Conclusions. Certain inferences are warranted by the facts that have been reviewed:

1. A careful balancing of the acids and bases of the urine gives us reliable indications of the presence of any considerable amount of acid foreign to the urine.

2. Many instances of dilatation of the stomach and of arthritis deformans show a considerable apparent excess of bases. A wider range of clinical observation would probably show an increase of this

kind in many different states of disease. This is probably true of many cases of acute gastritis, of cirrhosis of the liver and of phosphorus-poisoning.

3. In diabetes there is often a large apparent excess of bases over acids. This is due chiefly to the presence of β-oxybutyric acid, and to a less extent to diacetic acid.

4. The presence of β-oxybutyric acid in the cells and blood can probably be regarded as the cause of coma. This effect does not depend on specific properties of the acid, but on its action in reducing the alkalescence of the blood.

5. Organic acids introduced into the mammalian body withdraw alkali from it.

6. In slight grades of intoxication or acidosis, it is not always possible to say which bases are withdrawn in excess.

7. In well-developed intoxications ammonia is the chief base withdrawn; but where the quantity of this base is largely increased, sodium and potassium and even calcium and magnesium may be removed from the body.

MULTILOCULAR CYSTOMA OF THE PANCREAS.

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NUMEROUS cases of cystic tumors of the pancreas have been reported of late years, especially in consequence of the attention which surgeons have directed to lesions of the abdominal viscera. A critical review of the literature of the subject, however, makes it evident that the term pancreatic cyst has been used to indicate lesions differing in etiology, clinical characteristics, and in the results of treatment. Virchow (*Die Krankhaften Geschwülste*, 1863, i., 276) describes two separate varieties under the term *ranula pancreatica*. In the one the entire duct is widened and an ordinary rosary-like dilatation occurs; in the other the duct becomes dilated into a cyst, the contents of which may be slimy, hemorrhagic, or even calculous material.

Nearly twenty-five years later (*Berl. klin. Woch.*, 1887, xxiv., 248) he finds it no longer easy, especially when the cysts are large, to discriminate between the varieties of cystic tumor which may occur in the vicinity of the pancreas. He looks forward to the time, however, when the method of origin of the larger cysts may become more clearly established.

One of the most important contributions to the differentiation of the large cysts in the region of the pancreas was made by Jordan Lloyd (*Brit. Med. Journ.*, 1892, ii., 1051), when he maintained that such cysts might occur in consequence of an injury to this gland as a result of which the wall of the lesser omental sac becomes inflamed and an accumulation of liquid exudation is retained within its cavity. The simultaneous laceration of the pancreas permits the specific secretion of the gland to be mingled with the serous exudation of the omental bursitis.

Occasional instances of multilocular cystic tumors of the pancreas have been reported and have been described as simulating in gross

appearances and in structural characteristics the multilocular cystoma of the ovary. Bozeman (*N. Y. Med. Journ.*, 1882, xxi., 46), for instance, removed from the abdomen of a woman, aged forty-one years, a cystic tumor which Garrigues (*Med. Rec.*, 1882, xxi., 286) subsequently described. It consisted of a principal cyst holding two and a half gallons of brown liquid. The wall was trabeculated, the partitions contained large holes, and it bore several secondary cysts of the size of small hen's eggs. The walls were lined with cylindrical or polygonal epithelium, and the hardened section showed that the formation of the secondary cysts took place as in an ovarian cyst. The patient of Riedel (*Arch. f. klin. Chir.*, 1885, xxii., 994), a woman, forty-five years old, had a tumor in the upper abdomen for nine years, at first not producing any symptoms. In the last year and a half it had increased so rapidly in size that the entire abdomen was filled with a fluctuating tumor thought to be of ovarian origin. Laparotomy was performed and the cyst was punctured; ten litres of brown fluid escaped, and the tumor was removed. Death occurred four days later. The cyst had an adenoid projection from the wall, several globular spaces communicated directly with the interior, the spaces being lined with cylindrical epithelium, and others had papillary elevations, as in ovarian cystoma. Paltauf examined the body of a female patient of Salzer, aged forty-two years (*Zeitschr. f. Heilk.*, 1886, vii., 19). Death was due to cancer of the breast, but he found a tumor twice the size of a man's fist apparently continuous with the pancreas. Its contents were a thick, slimy, grayish-brown fluid. From the anterior and lower portion of the cyst projected two globular, lobulated masses, the one as large as an apple, the other the size of an egg. They were separated from the main cavity by widely perforated septa, and were composed of an aggregation of smaller cysts. The walls were lined with cylindrical epithelium, and the pancreatic duct was found within the gland.

In Kuhnast's case (*Inaug. Diss.*, Breslau, 1887), a man of fifty-one years, the body of the pancreas was found after death to be made up of cysts, one as large as a medium-sized apple. All the cysts were filled with blood in various stages of metamorphosis. Almost the entire gland was transformed into fibrous tissue and the dilated duct was to be traced here and there through the cystic portion.

The case reported by Martin (Virchow's *Arch.*, 1890, cxx., 230)

perhaps belongs in the same series. He successfully removed from the region of the pancreas of a woman, fifty years old, a cystic tumor which filled the entire abdomen. It had first been observed when she was twenty-one years of age, and then was the size of an egg. When the patient was thirty-four years old the tumor was as large as a man's head and was thought to be of ovarian origin. An exploratory laparotomy at this time showed the growth to be behind the transverse colon, and the wound was closed. At the final operation fifteen litres of a thick, brown fluid escaped from the cyst, which was isolated except at one end, where it was tied and cut away, leaving a stump about two fingers thick. A portion of the wall contained a large number of cysts varying in size from that of a hazel-nut to a goose egg. All were lined with cylindrical epithelium, and no pancreatic duct was found.

Gussenbauer (*Prag. med. Woch.*, 1891, xvi., 365) drained a cyst in the region of the pancreas of a woman, twenty-eight years of age. The tumor was first noticed two and a half years before the operation. It then was as large as the fist, but within the last six months had rapidly increased in size until it was as large as a man's head. Several months after the operation the patient died of phthisis, and Chiari made the post-mortem examination. He found a fistula extending from the abdominal incision to the pancreas, and the left half of the latter was replaced by a collection of cysts, the largest the size of a hen's egg. The smaller cavities were lined with a cylindrical epithelium. The pancreatic duct was open from the duodenum to the cysts.

Thiroloix and du Pasquier (*Bull. de la Soc. Anat.*, 1892, lxvii., 310) found nearly the whole pancreas of an elderly woman transformed into a mass of cysts—the largest the size of a hen's egg, the smallest less than the size of pease, the whole forming a tumor twice as large as a fist. There was no constriction of the duct of Wirsung.

Cibert (*Gaz. des Hôp.*, 1896, lxix., 347) reports the results of his examination of a cystic tumor successfully removed by Poncet from a woman, twenty-six years old. The growth first was noticed six years before the operation, and increased slowly for four years. Just before the operation it was apparently of the size of the head of an adult. A large cyst was found, in the wall of which were smaller cysts no larger than hazel-nuts. These were lined with cylindrical

epithelium, and the wall of the main cyst was traversed by long ridges enclosing communicating spaces.

The above series includes all the cases of benign multilocular cysts of probable pancreatic origin I have been able to collect. It is noteworthy that all, with but one exception, have occurred in women; that, as a rule, the growths have existed for a number of years without much change or proving a causing of disturbance; and that rapid increase in size is usually the result of the formation of a single large cyst.

The walls were lined with cylindrical epithelium, and the comparison between them and the ovarian cyst was often made. The statement of the microscopical appearances, however, is not sufficiently detailed to convince the reader that these multilocular cysts were other than retention cysts proceeding from the smaller branches of the duct of Wirsung.

The following case is reported for the purpose of confirming the view that a multilocular cystic tumor, presumably of pancreatic origin, may occur in the region of the pancreas, and belong to the group of proliferating cysts:

Mr. ——, thirty-six years of age, born in Maine, a carpenter and builder, was sent to me October 23, 1899, by Dr. C. D. McCarthy, of Malden, to whom he had been referred by Dr. Tenney, of the same city. There was no evident hereditary predisposition to disease, and the previous health had been excellent, there having been no serious illness since boyhood, when pneumonia had occurred. Syphilis was denied. He was temperate in the use of alcohol and a total abstainer from tobacco. Tea and coffee were used freely, and he was in the habit of drinking two or three glasses of water at his meals.

In the spring of 1899 he was in his usual good health, but in July he began to complain of a constant dull pain in the left lumbar region and extending into the dorsal region. It was worse when lying down at night, but was less discomforting when he lay upon his back. The pain gradually increased in severity, until at the end of two or three months it ceased, after the application of tincture of iodine for three or four days. Within the past month he has noticed in the left hypochondrium a swelling, which has increased a third in size during this time.

Throughout his illness he has not been obliged to restrict his diet, and the appetite has been good. During the past month it has been excessive, and there has been also marked thirst. Immediately after eating the food would seem like a weight in the stomach, and there would arise a sense of exhaustion, lasting for a few minutes, or even for a half hour. More or less

belching of gas would occur, a rumbling in the abdomen was frequently to be heard, and peristalsis in the epigastrium was occasionally to be seen. Of late he has had nausea at times, although vomiting is rare. The bowels have been constipated, but the dejections are not unnatural in appearance.

In the past week or two there have been attacks of palpitation, sometimes relieved by the expulsion of gas. During the same period he has felt faint and has looked pale for a while two or three times daily, and has suffered more or less from dull pain in the temples. He has no cough, but is somewhat short-breathed on ascending an elevation. His breath at times smells queerly.

During the past month he has been obliged to micturate six or seven times during the night, and then passes over two quarts of urine, although not more than a pint in the daytime. There is nothing abnormal in the appearance of this secretion. The skin has been dry throughout the illness, although during the summer months he would sweat at night. He has gained five or ten pounds in weight, but has lost so much strength that he has ceased work on this account. His legs easily tire, but his feet do not swell.

On physical examination the face was pale; temperature, 99° F.; pulse, 88; respirations, 20. The heart and lungs were negative, with the exception of the presence of a systolic murmur at the base and apex of the heart. The urine was 1044, alkaline, with a slight trace of albumin, but no sugar. The examination of the blood showed 4,912,000 red corpuscles, 10,000 leukocytes, and 70 per cent. of hæmoglobin.

The epigastrium and left hypochondrium were swollen and tense from the presence of a rounded resistant tumor extending downward and backward to the vicinity of the left twelfth dorsal vertebra, thence forward three finger breadths above the crest of the ilium toward the median line. The upper border as determined by dulness on percussion was as high as the left nipple. The lower border formed a sharply defined rounded surface. The tumor was elastic, of doubtful mobility, and presented a rounded prominence from the upper part just below the left lower costal cartilage in the mammillary line. A wave was to be recognized in the left portion of the tumor. The position of the mass behind the stomach was indicated by the overlying tympany in the upper epigastrium, with easy upward displacement of the gas, and by the ready production of a splashing sound in front of the upper portion of the tumor.

The patient was sent to the Massachusetts General Hospital for further observation. October 30, 1899, ten grammes of glucose were given in divided doses, but no sugar was to be found in the urine subsequently passed. After salol was taken no urine was voided for six hours; the specimen then examined gave the reaction characteristic of the presence of salicylic acid.

A diagnosis of cyst of the pancreas was made, and the patient was transferred to Dr. M. H. Richardson's ward for surgical treatment.

November 7, 1899. An incision seven inches long was made over the tumor, two inches to the left and parallel with the median line. The tumor

was found to occupy the region of the lesser omental cavity. A trocar was pushed through the wall and a considerable quantity of reddish-brown fluid escaped. It was apparent that the cyst was multilocular, the separate cysts, some of which were nearly as large as the fist, not being intercommunicable. The intervening septa were torn through, as much of the contents removed as possible, and the sac was then separated from the surrounding parts and detached. Diseased portions of what was supposed to be the pancreas, but having a malignant look, were removed with the tumor. Six weeks later the patient was discharged relieved. At the site of the wound was a sinus at least two inches deep, from which a slight discharge escaped into the dressings.

A portion of the liquid contents of the tumor was examined in the laboratory of Prof. E. S. Wood by his assistant, Mr. H. C. Smith, with the following result:

Quantity, 250 c.c.; color, dark-brown; sp. gr., 1022; reaction, alkaline. Considerable free blood present, but no pancreatic ferment.

Solids	7.32	per cent.
Urea	0.18	"
Albumin	1 66	"
Ash	0.81	"
Chlorine	0.32	"
Na.Cl.	0.53	"

Dr. W. F. Whitney received the fresh specimen and forwarded the following report:

"Hemorrhagic cystadenoma; a cystic mass the size of a squash, of a dark-red color, indicating extensive hemorrhages, with a very soft necrotic tissue mingled with dark-red fluid. No definite pancreas could be made out, though some of the hemorrhagic masses suggested a piece of the pancreas, and another an infiltrated adrenal gland. A little piece of the tissue was soft, grayish, and rather malignant-looking to the eye."

On microscopic examination of hardened and stained sections, rounded and irregularly sinuous cavities of various size were to be seen, some with incomplete septa, others with projecting papilliform growths. Some of the cavities contained granular, fibrillated, or hemorrhagic material; others were filled with papilliform growths grouped in a somewhat irregular manner. The contents were occasionally cellular, the cells being free or clumped, at times in tufts. Many of the cavities were lined with a cylindrical epithelium, which was more or less stunted in the larger cysts. Some of the papilliform growths bore a cylindrical epithelium, while others were covered with cuboid cells. Occasionally the distribution of the epithelial cells suggested the acini of the pancreas, but the normal structure of this gland was not seen in any of the sections examined. The connective tissue between the cysts in places was densely fibrous, while elsewhere it contained numerous cells and was composed of interlacing fibrils, the latter forming a meshwork

enclosing a more or less homogeneous intercellular substance. Large and thin-walled bloodvessels were numerous. In places granules of blood-pigment and agglomerated red blood-corpuscles gave evidence of old and recent hemorrhages, while extensive areas of necrosis, in which the structural details were well preserved, were not infrequent. It was in their vicinity particularly that the thin-walled bloodvessels and the hemorrhages predominated.

Although the above-mentioned characteristics prevailed in the sections examined, in a few of the latter a tendency to the atypical growth of epithelioid cells was apparent. The cells were of a cylindrical character, but by no means of a uniform shape, size and arrangement, and were grouped in a tubular form, but the tubules often were so closely approximated as to present an irregularly alveolate appearance.

The tumor, from its histological appearances, thus is to be regarded as essentially a multilocular cystoma, but on the border line between a proliferating cystoma or cystadenoma and a cystomatous carcinoma, a distinction which the subsequent history of the patient may be expected to make clear.

Combinations of cystoma and carcinoma in pancreatic tumors have been reported in rare instances. Hartmann (*Cong. Franc. de Chir.*, 1881, 618) records the case of a woman, fifty-three years old, who had suffered from digestive disturbances for some time, but within

three months had rapidly become emaciated and enfeebled. In this period there were abdominal pains, and a tumor appeared, seemingly as large as the two fists. Laparotomy was performed, and at the operation 200 grammes of brown, chocolate-like fluid were removed from the growth, which lay behind the stomach, and its cavity was drained. Death occurred some six weeks after the operation. At the autopsy the entire body and tail of the pancreas were found to form a polycystic mass, through which the pancreatic duct could be followed. Cancerous nodules were found in the liver, and Gilbert, who examined the cysts, regarded them as representing a cystic epithelioma, with the new formation of glandular cul-de-sacs presenting a cystic dilatation.

Reference is made in the article just mentioned to a work published by Hanot and Gilbert (*Etudes sur les Maladies du Foie*, Paris, 1888), where a case is referred to in which a series of cysts of various dimensions were found in the pancreas. The tumor was generalized in the liver, and Gilbert regarded it as a tubular pancreatic epithelioma.

THE UREA CONTENT OF THE BLOOD IN CASES OF NEPHRITIS.

By JOHN SEYMOUR THACHER, M.D.,
OF NEW YORK.

THE chemical pathology of the blood has been undeservedly neglected. Surely nothing is more fundamental in the consideration of a patient's condition than the chemical condition of the blood, and yet it is of the greatest rarity that a physician investigates the chemical composition of the blood of his patients. The morphology of the various organs, both gross and microscopic, has been studied with the greatest thoroughness, and of late years the morphology of the blood has received an abundant share of devoted attention, with the most important results. The newly-developed science of bacteriology has been extended to clinical observations of the parasites present in the blood, and the technique of examinations in this direction has been made so easy that with many physicians they are a regular part of clinical routine.[1] Physiological chemistry has not lacked a devoted host of able investigators, and clinically the chemistry of digestion and the chemistry of the urine have been most thoroughly studied, and to great practical advantage. But the clinical examination of the blood with reference to variations in its chemical composition has been almost entirely neglected. This has, of course, been due very largely to the difficulty of obtaining specimens in these days of infrequent phlebotomy.

A conviction of the importance of this neglected field has led me to consider the possibility of obtaining such specimens in some way convenient to the physician and free from danger or annoyance to the patient. I have found that it is not at all difficult by means of the simplest apparatus to obtain with great ease and in a manner usually arousing no objection on the part of the patient abundant quantities

[1] James and Tuttle. Medical and Surgical Report of the Presbyterian Hospital, 1898, vol. III.

of blood for quantitative chemical analysis. No more formidable apparatus is needed than a glass bulb or flask, with a short tubular projection, so ground that a small aspirating needle may be tightly fitted to it by slipping on, and with a second orifice stopped with a rubber cork through which a glass tube passes. To this glass tube is attached a rubber tube with a glass mouth-piece. The needle being inserted into a vein and suction applied to the mouth-piece, there is rarely any difficulty in speedily filling the bulb or flask with blood. The receptacles which I have used have a capacity of three or four ounces, and the shape which I have preferred has been that of an Erlenmeyer flask, the projection to which the needle is attached running out horizontally near the base, the rubber stopper being inserted into the ordinary opening at the top. It is desirable that this latter opening be large enough to allow the clots to be easily blown out of the flask when it is inverted. It is most important that the grinding for the attachment of the needle be carefully done, so that the joint shall be air-tight; and the success of the employment of this device depends chiefly upon the sharpness of the needle and the size and smoothness of the lumen. It is well to have the needle short as well as the projection to which it is attached, and to have the "fitting" of liberal size, so that the glass projection may be large enough to secure for itself strength and a large lumen. There should, of course, be no lateral openings in the needle. The size of needle which I have found most useful is from 20 to 23, Stubbs' gauge. It is naturally best that the needle be thin-walled, so as to combine a maximum of lumen with a minimum of total diameter. The veins which have seemed to me best adapted to this procedure are the median basilic and median cephalic, just in the flexure of the elbow.

Having tied a gauze bandage tightly around the upper arm, and having gently scrubbed the site of puncture, first with soap, and then with alcohol or ether, I quickly plunge the needle through the skin, and then, while exerting a continuous suction, find the lumen of the vein. When this is once found it is important to hold the arm and instrument as steady as possible, and to maintain a continuous flow by exerting a constant suction. After the needle is removed and the bandage loosened there is rarely even a drop of hemorrhage from the puncture. In some instances, where there has been difficulty in finding the lumen of the vein and there has been much prodding, a con-

siderable black-and-blue spot, and sometimes a little stiffness follow the procedure; but no further trouble has resulted in any instance. In most cases, however, a barely visible discoloration takes place, and a majority of patients show no dislike of the trifling operation. I have tried it upon myself, and find that with a sharp needle, even though a fairly large one, the prick of the stab is hardly painful.

Armed with this simple device, we have inaugurated at the Presbyterian Hospital the chemical study of patients' blood. So far we have only made a beginning, and my chief reason for bringing the matter before you now is to emphasize the importance and demonstrate the ease of obtaining these specimens, in the hope that this line of investigation may be actively developed and the accumulation of observations by numerous investigators may before long throw light on some obscure pathological questions, and lead to a better understanding and better treatment of many patients.

So far we have confined our studies to the urea content of the blood, and have determined the quantity of this substance in sixty-three specimens, several of which came from patients outside the hospital, through the kindness of their physicians. The method of determining the quantity of urea has been to make an alcoholic extract, and then use the hypobromite process. The blood is put through a wire sieve; forty drachms is, as a rule, then taken; three times that volume of absolute alcohol is shaken up with it, and the mixture allowed to stand for twenty-four hours. It is filtered and washed with hot absolute alcohol, and evaporated nearly to dryness. The residue is again taken up in absolute alcohol and filtered and washed. The filtrate and washings are again evaporated nearly to dryness, and the residue dissolved in a little water. Sodium hypobromite is then applied, and the nitrogen evolved represents, of course, all alcoholic extractives of the blood which liberate nitrogen under the action of sodium hypobromite; but, as urea constitutes nearly the whole of such substances, this method is thought to indicate the amount of urea closely enough for practical purposes.

The analyses in these cases were made by Miss Selma Granat.

A few parallel analyses were made to see whether the same results could be obtained if we used 95 per cent. alcohol instead of absolute in the first extraction. Five such parallels were put through, with the following results:

	Absolute.	95 per cent.
1	0.157	0.148
2	0.116	0.101
3	0.169	0.135
4	0.103	0.081
5	0.111	0.105

Showing that the 95 per cent. alcohol extracted a slightly less quantity of nitrogenous material by a fairly constant difference.

In only one instance were we able to compare the blood taken from the vein shortly before death with that obtained at autopsy shortly after death. In this case the blood taken from the vein a few hours before death contained 0.121 per cent. of urea and that obtained at autopsy, eighteen hours after death, by allowing it to flow from the great vessels at the base of the heart into the pericardium, contained 0.145 per cent.

In this group of observations there were but few on patients supposed to be in perfect health or beyond suspicion of nephritic complications.

No. 1. Man, aged forty-three years, in good health; moderate indigestion and moderate neurasthenia, 0.030.

No. 2. Girl, aged twenty years, with paraplegia, urine and heart normal, 0.021, and three days later, 0.024.

No. 3. Man, fifty-six years of age, with normal urine and normal arterial tension; has the appearance of moderate anæmia, some dizziness, and some mistiness of vision, 0.053.

No. 4. A woman with jaundice and a slight degree of œdema, and at times a faint systolic murmur over the præcordium, but nearly normal urine, 0.014.

No. 5. Six days after the crisis of pneumonia, the urine being normal, 0.025.

These six observations upon five patients, giving figures ranging from 0.014 to 0.053, though small in number, agree in a general way, with those of other observers, in indicating the normal percentage of urea.

Forty determinations of urea have been made in the blood of twenty-one cases of well-marked nephritis. The results, with some of the more prominent symptoms, are noted in the following table, where the cases are arranged in order according to the abundance of urea. The more conspicuous symptoms are presumably absent when not noted:[1]

[1] For the blood-pressure determinations, obtained by the Hill-Bernard sphygmometer, I am indebted to Dr. H. S. Carter.

No.	Sex and age.	Complications.	Acute or chronic	Casts.	Albumin.	Œdema	Vomiting.	Dyspnœa.	Tension observed by finger increas'd.	Blood pressure.	Headache.	Insomnia.	Delir'm or twitching.	Conv'lsions.	Coma.	Improved.	Urea per ct. in blood.
6	M. 50	Enlarged liver; ascites.	Chron.	g +	absent at times	slight	o	+	+	152 155 150 155 140	+	.....	+	.....	partial	o	0.032
7	F. 47	.....	Chron.	+	×	.....	+	+	×	.....	+	+	.....	o	o	o	0.033 0.036
8	F. 23	Endocarditis, hydrothorax.	.....	×	×	.....	.....	+	o	155 125 130 115 140	+	.....	.....	.....	.....	.....	0.030 0.013
9	F. 50	.....	.....	1 few at times	1 scant +	.....	.....	+	+	.....	.....	.....	.....	+	partial	.....	0.057
10	F. 49	.....	Chron.	+	× at times	slight	+	at times	slight	.....	+	.....	+	o	o	.....	0.060
11	M. ...	.....	.....	o	trace	.....	o	×	×	.....	.....	.....	+	.....	.....	×	0.066
12	F. 30	Abort. just previous.	Acute	×	×	×	.....	.....	.....	.....	.....	.....	.....	+	.....	×	0.077
13	M. 59	.....	Acute	+	×	consid.	o	+	×	160	.....	.....	.....	.....	.....	.....	0.090
14	F. 31	.....	Chron.	.....	g scant	.....	+	.....	o	.....	+	.....	.....	+	.....	.....	0.083
15	M. 52	.....	Chron.	few	abund.	×	+	+	1 × 1 less	.....	+	+	.....	.....	.....	.....	0.111 0.080
16	F. 62	.....	Acute	+	+	1 o consid.	o	+	1 much g slight	.....	o	.....	.....	.....	.....	.....	0.115
17	M. 22	.....	.....	at times × at times o	g scant at times ×	.....	+	.....	+	122	.....	.....	.....	+	.....	×	0.120
18	F. 62	.....	.....	few	scant	o	.....	+	+	.....	+	.....	.....	.....	apathetic at times	+	0.116 .081 0.108 .144 0.119
19	F. 40	.....	Chron.	+	×	slight	+	o	×	.....	+	.....	.....	o	o	.....	0.131
20	F. 24	Endocarditis	.....	o	.....	consid.	.....	+	+at times	.....	.....	.....	.....	.....	.....	.....	0.133
21	M. ...	Cerebellar hemorrhage	.....	.....	abund.	.....	.....	.....	.....	.....	.....	.....	.....	+	.....	Died	0.121 0.145
22	F. 24	.....	.....	g +	scant at times ×	slight	×	.....	at times	119 110 100 110 108 105	+	.....	.....	.....	.....	+	0.208 .165 0.172 .034
23	M. 32	.....	Chron.	+	+	consid.	.....	+	+	.....	.....	.....	.....	.....	.....	.....	0.194
24	M. 30	Endocarditis	Chron.	few	g trace at times ×	consid.	+	o	×	155 160 110 155 155 200	+	.....	.....	.....	.....	worse	0.019 .157 0.107 .169 0.128 .244
25	M. 21	.....	Chron.	+	×	+	o	.....	+	.....	+	+	.....	.....	.....	.....	0.233
26	M. 33	Endocarditis	.....	g o at times	abund.	+	+	+	+	135 138 145	+	.....	+	.....	.....	Died	0.026 .411 0.045 .340

+ present. o absent. × much or marked. g generally, l later.

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the twenty-one
., and in two of
other days. So
excess of urea in
enever examined.
reached 0.110 per

s here reported any
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not. A much longer
wers to such questions.
acute (Nos. 12, 13, and
90, 0.077, and 0.115 per
list.
on of typical cases of uræmia
ulsions, the urea content of the
normal limits." In five of my
nvulsions were noted. Of these
(0.121 and 0.120 per cent.), two
0.077 per cent.), and one was close
rcentage (0.057 per cent.).
show a good deal of œdema give these
1 per cent., later 0.080 and 0.089 per
0.244 per cent.—that is, to quite a high

this list had a distinct increase of arterial ten-
d by the finger or by the sphygmometer. But
did not regularly follow the richness in urea. In
in which the urea gradually rose from 0.089 to
the pressure, after wavering about 155 to 180, finally

cases in which the urea was very high, say
serious condition, and such high figures
to get a better view of the seriousness

of the case and of the nature of the trouble. Those patients who died or were recorded as becoming distinctly worse are found toward the bottom of the list. But, on the other hand, it is equally clear that a low percentage of urea is found in some severe cases of nephritis. A few cases quite miserable with symptoms which seemed to be purely nephritic contained in their blood only a normal amount of urea. Some patients, however, with little urea had complications which should be taken into account.

It has been interesting and instructive to watch the changes in the urea content in certain cases. I will give these changes in five cases, in which we made a number of analyses, and will ask you to notice their courses clinically and chemically.

No. 22. A young woman, twenty-four years old, who came to the hospital complaining of epigastric pain, vomiting, and hæmatemesis. Her urine was found to contain albumin and casts. She has improved greatly and pretty steadily. The blood contained: April 4th, 0.208 per cent. urea; April 6th, 0.172; April 9th, 0.165; April 27th, 0.034.

No. 18. A woman of sixty-two years, who came in complaining of headache and dyspnœa. She was in an apathetic condition. The urine contained albumin and casts. She improved quickly, and then remained about the same. Her blood contained: April 12th, 0.116 per cent. urea; April 16, 0.103; April 20th, 0.119; April 21st, 0.081; April 29th, 0.144.

No. 24. A man, thirty years old, with a chronic history of œdema, headache, dizziness, and vomiting. He had murmurs of valvular lesions, and in his urine albumin and casts. His condition has been somewhat variable, but lately has been worse. His blood contained: March 22d, 0.089 per cent. urea; March 30th, 0.107; April 6th, 0.128; April 11th, 0.157; April 16th, 0.169; April 27th, 0.244.

No. 26. A man, thirty-three years old, with a chronic history of œdema, dyspnœa, headache, vomiting, and diarrhœa. He had endocarditic murmurs. His urine contained albumin, and on one examination out of four contained casts. He developed a muttering delirium, gradually sank, and died. His blood contained: April 4th, 0.326 per cent. urea; April 6th, 0.345; April 9th, 0.411; April 13th, 0.340.

In fourteen additional cases in which albumin or casts, or both, were present in the urine, but where the nephritis seemed to be not an important part in the patient's condition, the figures for the urea were 0.030, 0.033, 0.041, 0.046, 0.046, 0.053, 0.054, 0.057, 0.069, 0.072, 0.073, 0.074, 0.075, and 0.108 per cent. The last case was a diabetic in coma.

A MODIFICATION OF THE SPHYGMOGRAPH.

By ROBERT T. EDES, M.D.,
OF BOSTON.

THE sphygmograph is an instrument which I believe has never been held in high respect by the physiologists. It is unnecessary to analyze all its defects and inaccuracies in the various forms in which it has appeared. This has been very thoroughly done by Baumgarten in Wood's *Reference Hand-book.*

But, notwithstanding these, it has always had a certain attraction for the clinician, because it gives a record more compact and less subject to personal error, if not more delicate, than even the well-trained finger.

It is useless to expect from it pathognomonic indications of valvular disease, but, with care, it can be made to show certain conditions of the blood-pressure that are, if not more easily detectable, at least more easily demonstrable in this way, and which are very useful in studying and recording diseases, disorders, and the action of remedies, especially such as involve the vasomotor system.

A clinical sphygmograph must be convenient and not require a tedious adjustment of pads, straps, and support, and it is this virtue which has made the "Pond" instrument, when used without the arm-rest, so popular in this country. But the "Pond" is defective in the following points:

The resistance to the tension of the artery should be by a spring and not by weight, so far as possible, because the error due to *vis inertiæ* is less, and also because, unless the instrument is held exactly upright, which is not always easy at the bedside, the levers are not working at all times under the same conditions.

The spring should be a metal one. Rubber springs are constantly changing by time and readjustment.

The pressure used should be simply the pressure of the pad on the artery, or as nearly so as possible, and not the pressure of the base of the instrument on the adjacent tissues. Of course, no sphygmograph to be used on the human subject can be free from the modifying effects of the tissues *super*jacent to the artery which may, equally, of course, vary a good deal with the elasticity of the skin and the amount of connective tissue present. The base of the "Pond" is so broad that when the little metal disk within the rubber cap is pressed down on to the radial the graduation on its stem indicates not the pressure over the artery, but that of the metal cap upon the edge of the radius, the flexor carpi radialis, or both. It is also very desirable that the tracing should itself be a record of the pressure at which it is made.

This roughly-made instrument which I have here indicates, I think, how some of these defects can be remedied.

Some years ago I made and published a short account of a sphygmograph with a single lever, in which the tracing taken, which, of course, was only slightly multiplied, could be further enlarged by the use of a cylindrical lens.[1] As one might say, the amplification usually accomplished by a second lever was here done by a beam of light. The objection to this was that the tracing could not be used for demonstration without the glass, and could not easily be recorded for convenient use.

This slightly magnified tracing, however (only two and a half or three times), when taken on the same slip with the usual more highly magnified one, is useful for comparison with it. It throws out a certain amount of instrumental error dependent on looseness of joints and on acquired velocity of the most rapidly moving parts. A too delicate action of rapidly moving levers carries the writing-point beyond its proper mark in each direction.

A very beautifully constructed instrument shown me some years ago by Dr. Hopkins, of Buffalo, was open to this objection in the highest degree, and gave traces which indicated an amplitude of movement considerably beyond that of the arterial wall.

Elasticity and a want of rigidity in the levers has very much the same effect.

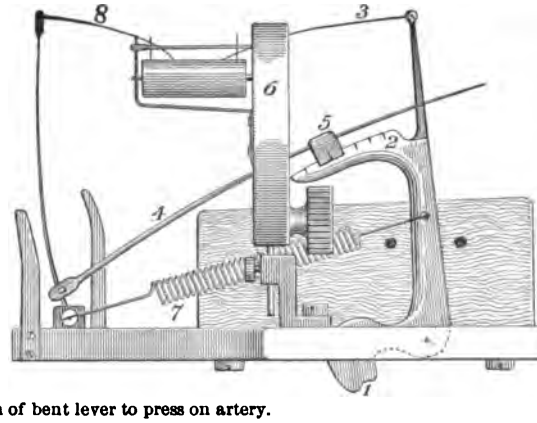
If a very long lever, multiplying the necessary number of times

[1] Journal of the American Medical Association, August 18, 1888.

(say twenty) could be made absolutely rigid and extremely light, then a sphygmograph somewhat like that described, but using a slip of paper wide enough to register all pressure, would be the ideal one.

In the modification which I now present I have endeavored to combine the essential points of magnification sufficient to be read without a glass, the easy and convenient applicability of the "Pond," the observation and recording of actual pressure over the artery alone, and the diminution of some instrumental errors. It consists of a bent lever, of which one end rests on the artery and the other carries a writing needle. It is held by a spiral spring. Pressure upon the

FIG. 1.



1. Short arm of bent lever to press on artery.
2. Notched arm.
3. Wire pen writing on slip between rollers of clock-work 6.
4. Adjustable connecting rod with 5.
5. Catch holding to one of the notches in 2.
6. Clock work.
7. Spiral spring.
8. Second lever multiplying the movement of the first lever several times.

The lever is represented as adjusted for a high pressure.

artery is made and changed simply by the amount of force employed by the hand which holds the instrument, the pressure upon the other tissues of the wrists having no effect upon the tracing except through the lever. This slightly magnified trace indicates by its position on the slip the amount of pressure on the end of the lever placed upon the artery, and the amount of movement is sufficient to allow the amplitude of the wave to be estimated and the best pressure for development to be selected. It can be made more distinct by the use of

the cylindrical glass. The range of pressures, with the spring now on the instrument, on a slip of the usual width is from 75 to 250 grammes.

FIG. 2.

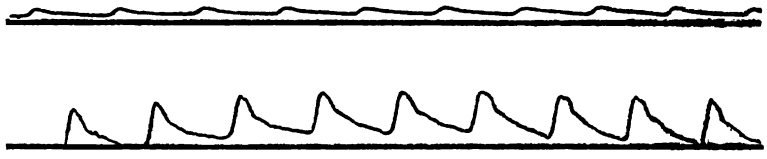


FIG. 3.

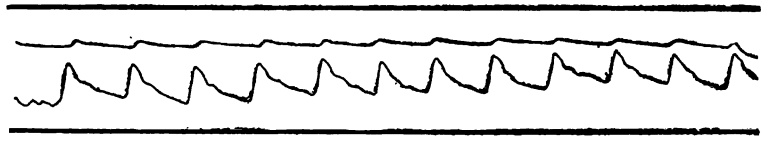


FIG. 4.

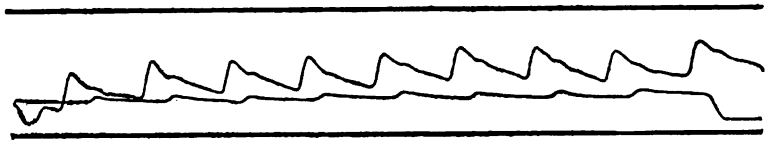
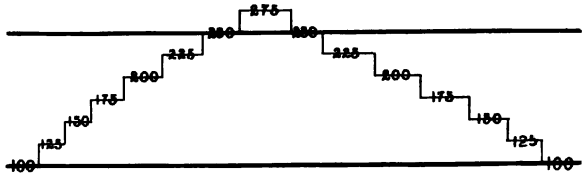


FIG. 5.

FIG. 6.



Four sphygmograms (Figs. 2 to 5) of the same pulse with varying pressures, the exact amount of which in grammes can be ascertained by comparing the position of the slightly magnified curve with the scale (Fig. 6).

The position of the highly magnified curve on the slip is of less consequence, as it corresponds to very slight variations in pressure within narrow limits.

The heavy lines parallel to the edges of the paper are made by the rollers which guide it.

The second lever, multiplying considerably more, does not have a fixed connection with the first, but by means of a notched arm is attached to it when the degree of pressure at which the tracing is to be taken is to be determined. The pressure can be varied a little, even after the two levers are connected, without throwing the writing-point off the smoked slip.

We have, then, on the slip two tracings, one magnified three and a half times, showing exactly the pressure and the amplitude at that pressure and free from exaggeration; and the second, corresponding to the only one usually given, which brings out the minuter form of the pulse-wave.

As I am now presenting this combination rather as a suggestion than as a finished instrument, I can speak of some points which might be improved in the hands of a better workman than I am.

I overheard a hardware salesman say, with considerable emphasis, to a customer who thought he could buy a spring to suit him ready-made, "Making a spring is an *art*." It is one which I do not possess either in theory or in practice. Although the spiral spring which I have here covers, I think, most ordinary ranges of pressure, yet I presume it would be possible to temper a steel spring so as to do much better and make a paper of the ordinary width record a range from nearer zero to a considerably higher point than this.

But that which I found most difficult to arrange satisfactorily looks, at first sight, so exceedingly simple that it seems almost silly to speak of it—that is, the catch between the two levers, which should be very light, very easy and quick of adjustment, without any slip, and, on the other hand, without friction or stiffness.

A REPORT OF TWO CASES OF FILARIASIS. OPERATION FOR LYMPHATIC VARICES AND CHYLOUS HYDROCELE, WITH REMOVAL OF ADULT WORMS.

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AND

JOSEPH H. PRATT, M.D.,

OF BOSTON.

FILARIASIS is a parasitic disease which is very common in many tropical countries, in some of which it is a scourge. In northern countries it is rarely encountered, and its numerous manifestations, consequently, are but little understood. It is probable that cases are repeatedly unrecognized.

The nature of the first case which is here reported was not recognized when he entered the hospital. The reasons are: first, because the disease was not suspected, and second, because the lesions which he presented at that time were not characteristic, so that under repeated similar circumstances there would be no objective signs particularly suggestive of filariasis, and only a blood examination would be positive. Consequently, we have decided to present the features of these cases as we encountered them.

CASE I.—On September 20, 1899, C. A., twenty-two years of age, entered one of the surgical wards of the Boston City Hospital with the history of the sudden onset of pain across small of back while lifting a bale of paper. This pain increased in severity, so that at the end of half an hour he could not remain standing, nor could he lie in one position any considerable length of time. The pain extended around to the left groin and down into the left testis. There was a desire to urinate frequently, but micturition did not give any relief. He felt dizzy and nauseated, but did not vomit. His temperature was normal. The urine was normal. Physical examination was negative.

The condition of the patient at this time was not such as particularly to attract the attention of the visiting surgeon. Two days later all of his subjective symptoms had disappeared, and he was discharged from the hospital feeling perfectly well.

He resumed his work as a bookkeeper, but soon noticed that there was a swelling in the left side of scrotum which extended up to the groin. This swelling disappeared on lying down. There was some discomfort when he was walking about, he got tired easily, and his condition was a source of worry to him.

On account of this swelling he entered the hospital a second time, and became a patient on the service of Dr. H. L. Burrell, and was then seen by the writers for the first time.

Sufficient examination was made to show that the left testicle was somewhat enlarged, but not tender, and that the cord was thickened by the presence of a mass of vessels which led to the external abdominal ring. On lying down these vessels decreased in size, and clinically corresponded to a case of varicocele. The external abdominal ring admitted the finger-tip readily, and there was a marked impulse and a slight hernial protrusion on cough.

His condition seemed to correspond to a varicocele complicated by a small inguinal hernia, and without particular attention being paid to his history, and without making further examination he was prepared for operation.

Under ether the usual incision for inguinal hernia was made and the cord exposed from the internal ring to the testis by drawing the latter toward the lower end of the four-inch incision. A small hernial sac was isolated and ligated, and the posterior wall of the inguiual canal restored in the usual manner. The cord itself was about the size of the index finger and was composed of about ten thick-walled tortuous vessels or tubes, in addition to the usual structures. There were two or three large veins to be seen which could be recognized by their dark color, but the remaining structures were light-colored and about the size of the veins in a varicocele. They were considerably distended and their walls were thick. It was decided to excise this mass of vessels for the whole length of the cord as in a varicocele operation. On dissecting this mass from the surrounding structures it was noticed that minute quantities of a thin, milky fluid appeared in the field of operation. Unfortunately at the time this fluid became mixed with blood and could not be collected. The appearance of this fluid and the color of the excised tubes were the features that first made us suspect that there was something unusual in this case. The hernia and varicocele operation was completed and the wound closed.

The patient recovered well from the operation and the wound healed by first intention.

Pathological Report of Excised Mass: Macroscopic examination by Dr. Howe. "The specimen consists of a mass of dilated vessels and some fat. It is 12 cm. long, 1 cm. across, 0.5 cm. thick. The vessels have firm, thickened walls, and do not collapse on being cut across. The largest vessels have a diameter of 2 mm." Microscopic examination: "Dilated and thickened veins."

PLATE I.

FIG. 1.

FIG. 2.

FIG. 3.

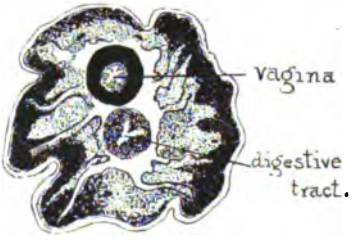
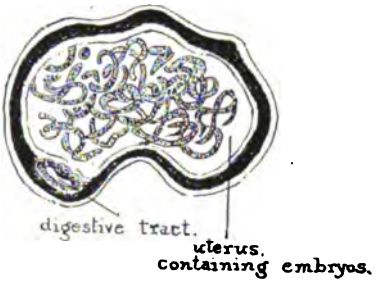


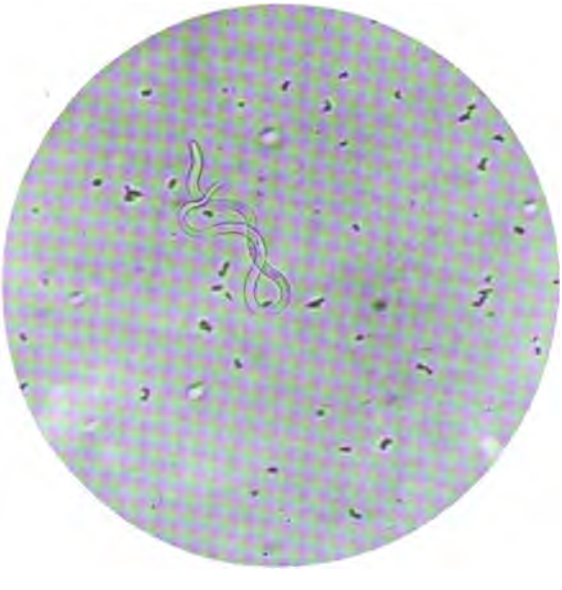
FIG. 4.



Cross-sections of an adult female filaria Bancrofti. Highly magnified.

Fig. 1, head. Fig. 2, body, 0.64 mm. from anterior end. Fig. 3, body, 1.26 mm. from anterior end. Fig. 4, body, anterior to bifurcation of uterus.

FIG 5.



Photomicrograph of a living filaria embryo in hydrocele fluid. Magnified 250 diameters.

The future history shows that these structures were not veins, although they resembled them under the microscope, and some of them contained blood. At the time of operation we felt certain that they were not veins on account of their light color when contrasted with veins near by, and the escape of small quantities of milky fluid.

Progress of case: *December 5th.* Stitches out, linear scar healed by first intention; no redness, tenderness, or induration. For two weeks longer the patient remained in bed and wore a protective dressing. Meanwhile there was a gradually increasing swelling of the left side of the scrotum, which was examined carefully on December 19th.

The skin of the scrotum was normal, and consequently showed no signs of redness or thickening. The swelling was larger than a hen's egg and globular. It was smooth, fluctuant, and not tender, and transmitted light as freely as an ordinary hydrocele. At the upper end of the tumor could be felt the stump where the cord was excised. The tumor was aspirated with the following result:

Pathological Examination by Dr. Low: "Specimen consists of about 90 c.cm. of opaque, chrome-colored fluid, which microscopically shows large numbers of embryo filariæ in active motion. There are numerous small round cells, a few red blood-corpuscles and oil globules, and a large amount of fatty granular material."

Chemical Examination by Dr. Ogden: "Reaction neutral; specific gravity 1018; albumin, 1.5 per cent.; fat, 1.53 per cent.; chlorine, 1.95 per cent. The fluid was completely clarified by shaking with ether after the addition of sodic hydrate. Diagnosis: Chyle in an inflammatory serous fluid."

19th, 7 P.M. Blood examination shows many filariæ. Differential count of leucocytes made by Dr. Steensland:

Small lymphocytes		35.33 per cent.
Large lymphocytes	3.00	
Transitionals	0.67	3.67 "
Polymorphonuclear leucocytes		56.67 "
Eosinophiles		4.33 "
		100 per cent.

300 leucocytes counted.

20th. Blood from ear examined at 3.15 P.M.; no filariæ found in four slides. 5.15 P.M. Patient has been in bed one hour; seventeen filariæ counted, with aid of movable stage, in each of two large drops.

The diagnosis was now firmly established and the obscure features of the case were easily explained.

At the time of operation he had a small inguinal hernia. The condition resembling varicocele was a collection of dilated and thickened lymph vessels, which extended into the testis, thereby increasing its size. There was no fluid in the tunica vaginalis testis until after the operation, and its appearance is readily explained by the fact that most of the return lymph vessels

had been excised. The tumor in the scrotum following the operation was a chylus hydrocele, for the most part, but was also due to the increasing size of the testis in consequence of the dilating of the obstructed lymph channels.

Previous History: It was known at entrance that this patient had lived on the Island of Barbadoes, and when questioned as to his past history, he said nothing about any previous sickness, and there was nothing observed that led us to suspect that we were dealing with a case of filariasis. The disease is so rare in northern latitudes that it is not suspected and its clinical manifestations are but little understood. The commoner symptom, chyluria, was absent, and the urine was normal. Furthermore, the patient, who is a fellow of considerable intelligence, knew that he had suffered from filariasis, but said nothing about his past history because he thought his present condition had nothing to do with any previous sickness.

We then obtained the following history:

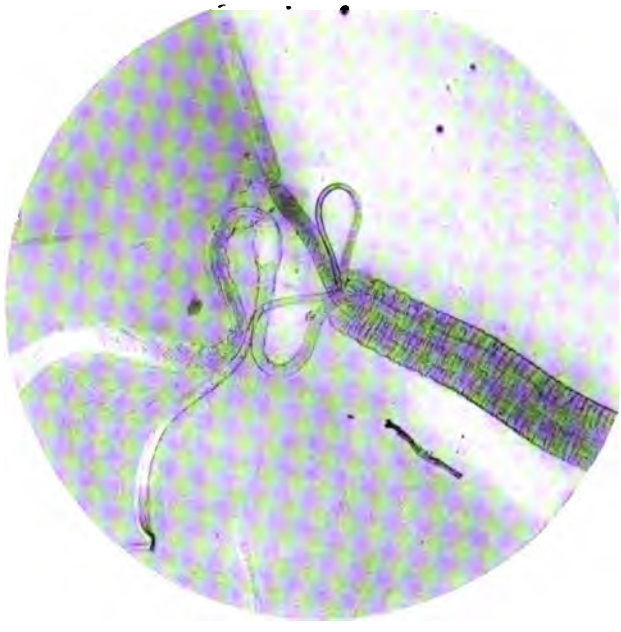
He was born on the Island of Barbadoes in 1878, where he lived for seventeen years. He was on his way to school one morning in September, five years ago, when he was seized with sudden pain across the lower back and lumbar regions and also in the left groin. It was so severe that he thinks it caused him to faint. He was carried home and put to bed. This is the first sickness that he can recall. This attack of pain was followed by a chill, which, in turn, was followed by others. There was more or less nausea and headache. He was given quinine and arsenic for a period of three months, and remained in bed for five months. During that time he was not very sick, but suffered mostly from weakness and debility. He had recurrent febrile attacks, during which the glands in the left groin were swollen and the left testis was enlarged. The glands remained swollen for about three months, but the testis became permanently enlarged. Chills and febrile attacks lasted about three months, with decreasing severity. During this period he was troubled with persistent drowsiness by day. Even up to time of operation drowsiness has been a feature in his case. His attack was diagnosed at the time as "Barbadoes fever," also called "fever and ague," and was understood to be due to filariæ. He remained in bed for such a long period, although not very sick, on account of the prevailing opinion that lymph scrotum and elephantiasis are thus avoided.

Ten months after the first attack he had a second one, which came on suddenly, and he was more or less prostrated for a month. The swelling of the left inguinal glands recurred, accompanied by the same constitutional symptoms. This time the glands were tender and the skin over them reddened. The testis gained in size, but became smaller later. He was not allowed to walk during this month.

On recovering from this attack he went to Montreal, Canada, and continued to go to school for about two years. Then he went to New York, served a brief period as a bookkeeper, and enlisted in the militia, and then spent some months in South Carolina. Somewhat over a year ago he came to Boston, where he was occupied as a bookkeeper.

PLATE II.

FIG. 6.



Portion of an adult female filaria Bancrofti, showing the digestive tract and the two uterine tubes extruded from the cut end. Magnified 38 diameters.

FIG. 7.

Large lymphatic vessel nearly occluded by an ingrowth of granulation tissue and containing two portions of an adult filaria Bancrofti. Magnified 38 diameters.

During this period of about four years since leaving the Barbadoes he has never been perfectly well and strong, but he has never had a severe attack similar to those from which he suffered at home. On an average of about once a month he would have a chill, followed by moderate fever for a few days. There would be a dragging sensation in the left groin, but no particular pain, and he felt languid and unable to work. At times there was pain in the back. It was one of these attacks that caused him to enter the hospital in September, but as he attributed the condition to heavy lifting, and was apparently well in two days, the true cause was not detected.

On leaving the hospital he resumed his work, but found that he got tired easily and could not work regularly, and was becoming discouraged. He had made up his mind to return to Barbadoes, when he had another attack of pain in the back and left groin, followed by increased malaise and mental depression, and he entered the hospital again, when we saw him for the first time. All of this history, however, he carefully avoided telling us, thinking that it had nothing to do with his present complaint.

21*st*. *Second Operation*. Having established the diagnosis beyond question, he was advised to have this whole tumor mass in the left scrotum removed, if thought advisable at the time of operation, and he readily consented. On the morning of the operation there were no embryos found in the blood. The skin of the scrotum was still perfectly normal and the inguinal glands were not enlarged nor tender. The tumor mass, which consisted of the left testis, together with some fluid in the tunica vaginalis, was not tender.

Under ether narcosis the original incision was extended a short distance on to the scrotum, the skin dissected from the tumor, and the whole mass removed without cutting into any part of it. The wound was closed without disturbing the site of the first operation. At 9 P.M. no embryos were found in the blood.

So far as the wound was concerned the patient made an uninterrupted convalescence.

Examination of the Excised Tumor. The specimen consists of a testicle with the intact sac of the tunica vaginalis. The mass is ovoid in shape, 10 cm. long, 6.5 cm. wide, 4.75 cm. thick. The sac contains about 50 c.cm. of a yellow semi-opaque fluid. The tunica vaginalis is smooth and glistening. The parietal layer is slightly thickened and semi-opaque. The spermatic cord at the point sectioned is 1.5 cm. in diameter. Near the testicle it enlarges greatly, measuring 5 cm. in thickness. Between the cord and the globus major is a soft wedge-shaped mass 3 cm. in width, composed of translucent distended vessels and œdematous fat. The testicle weighs eighty grammes. The globus major is greatly enlarged, measuring 3 cm. in width. It is soft, almost gelatinous, and its surface is marked by tortuous dilated lymph vessels averaging 1 mm. in width. The globus minor and the body of the epididymis are nearly of normal size. The testis propria measures 5.5 x 4 x 3.5 cm. It is very œdematous. The tubules tease out readily. The testicle is sectioned in its long diameter After a few minutes' inspection of

the cut surface a writhing coil, 6 mm. in size, is discovered upon the body of the epididymis. A single thread 1.5 cm. long extends from this mass across the mediastinum testis. A free end projects from the top of the coil. Half a cm. nearer the inferior border of the testicle is a smaller mass. The worms are white, opaque, and thread-like. When the testicle is immersed in warm, normal salt solution the writhing and the coiling of the worms is quite active. When detached from the surface by gentle manipulation they quickly anchor themselves to the surface again. Another tightly-coiled bunch is soon seen gradually to rise into view near the mass first discovered.

It was subsequently found that this third mass consisted of six worms, two males and four females. One of the males was complete. Of the others only their heads and portions of their bodies, varying from 1 to 4 cm. in length, were obtained.

In salt solution the movements of the worms continued over six hours—*i. e.*, until 11 P.M. The next morning all were dead.

The two masses first discovered presented the appearance shown in Plate III., Fig. 8, I. and II. They were carefully detached from the testicle and preserved in 5 per cent. formalin. Each mass consists of a single female worm. The pointed tapering anterior end is well shown in Plate III., Fig. 8, I. When the testicle was incised the bodies of these worms must have been cut and the prolapsed uterine tubes and digestive tract then became inextricably intertwined with the coils.

The following morning an entire female worm was discovered by Dr. Mallory on the outer surface of the testicle. It had evidently crawled out of the tissue into the warm salt solution. When found it presented the appearance shown in the photograph (Plate III., Fig. 8, III.).

22*d*, 5 P.M. A few filariæ found. Blood examination by Dr. Steensland: 8000 leucocytes, 6,016,000 red blood-corpuscles.

Differential count:

Small lymphocytes		38.2 per cent.
Large lymphocytes	0.2	
Transitionals	1.2	1.4 "
Polymorphonuclear leucocytes		55.8 "
Eosinophiles		4.6 "
		100 per cent.

500 leucocytes counted.

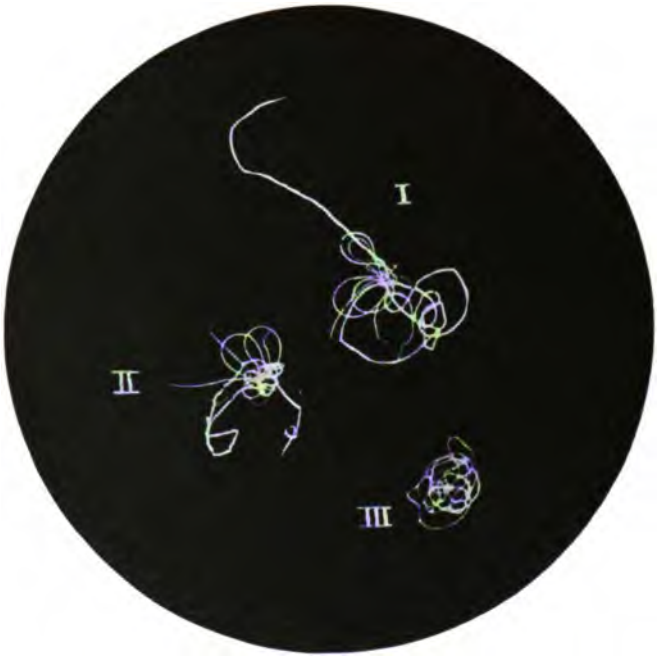
23*d*, 8.30 P.M. Fourteen filariæ found in one drop of blood, eleven in another.

Hæmoglobin	93 per cent.
Leucocytes	7400.

26*th*. Patient is suffering from pain in the right ear, from which there is a moderate amount of serous exudate escaping. Diagnosis: Acute otitis media. No embryos found in the exudate.

PLATE III.

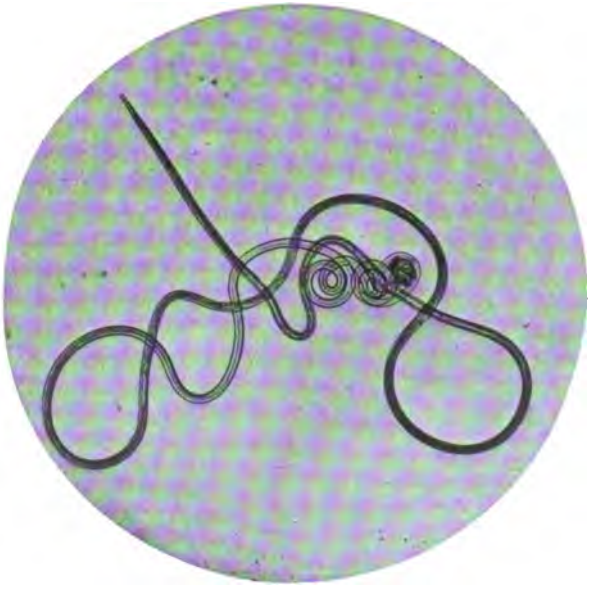
FIG. 8.



Female filariæ Bancrofti. Twice natural size.

I. and II. Two coils as they appeared on the cut-surface of the testicle. Each consists of a single female worm, somewhat mutilated; their bodies have been cut in two and the uterine tubes and digestive tract have been extruded. III. Complete female worm.

FIG. 9.



Adult male filaria Bancrofti. Magnified 10 diameters.

30th. Feces examined; no Charcot-Leyden crystals or other abnormal constituent found.

A simple method was devised for obtaining drops of blood of known size. A Thoma-Zeiss pipette for red corpuscles was used and blood drawn up to the mark 1 on the pipette. Then the blood was blown out upon a cover-slip.

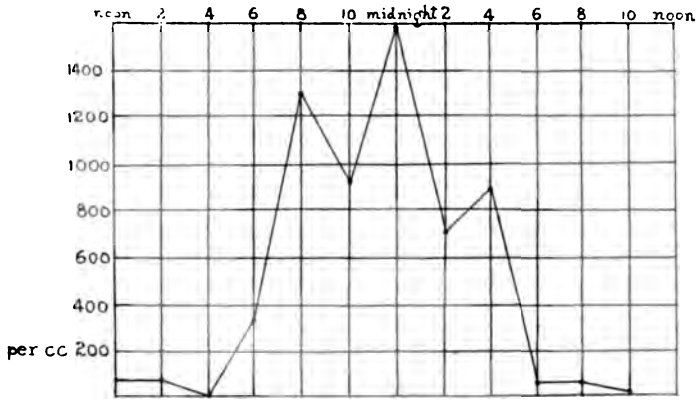
The "red counter" had a capacity of 1.2 c.cm. when filled to the mark 101. Hence, the standard drop we used contained 11.9 c.mm. of blood.

The average number contained in two drops was taken, and the number of filariæ in each c.cm. of blood calculated.

31st. At 8 P.M. the blood contains 438 filariæ per c.cm.

January 3d. Beginning at noon yesterday, two hourly counts were made for a period of twenty-four hours by Drs. Low, Fulton, and Steensland. The accompanyiug chart shows the nightly increase and decrease of filariæ in the

CHART.



Number of filariæ in cutaneous circulation.

peripheral blood. One slide, made at midnight, contained twenty-five filariæ, the equivalent of 2100 per c.cm. This is the largest number we have ever found.

The ear has become normal in every respect.

9th. Leucocytes, 3500.

Differential count:

Small lymphocytes		37.0	per cent.
Large lymphocytes	4.0		
Transitionals	4.5	8.5	"
Polymorphonuclear leucocytes		51.0	"
Eosinophiles		3.5	"
		100	per cent.

200 leucocytes counted.

15th. Patient discharged from hospital. The wounds are healed firmly, and there are no signs of any trouble at the site of operation.

June 1st. Patient rested a month after he left the hospital and gained strength rapidly. For the last three or four months he has been working as an orderly at the hospital, a position which requires heavy lifting and considerable hard work.

Since operation he has worked regularly. He has had no recurrence of the old pains in the back and left groin, nor have the chills recurred. He has gained in strength, and is no longer troubled with periods of general weakness, malaise, and mental depression.

The embryos still persist in his blood.

CASE II.—This man is a younger brother of the patient just considered, and he was asked by us to come for an examination more from curiosity than with the idea that embryos would be found.

He is twenty-one years old, was born in Barbadoes, and left the island with his brother, and they have been together more or less since. As a rule, he has always enjoyed good health and has always been able to go about and attend to his work. He has never had malaria, but occasionally he has suffered from what he calls "bilious attacks." He has never had any symptoms or manifested any objective signs which could with any degree of certainty be attributed to filariasis. The patient walked to the laboratory at 8 P.M., and the examination was made at once.

It was found that his blood contained numerous embryos of the filaria nocturna, showing that adult worms must be present in his deeper lymphatics, although there is no clue as to their location.

He feels perfectly well in every respect, and his case has not been studied further.

HISTORY. Demarquay[1] discovered in Paris in August, 1863, the embryos of filaria Bancrofti. The patient, a young man, a native of Havana, suffered from a chylous hydrocele, in the fluid of which the filariæ were found. Lemoine, who made the microscopical examination, writes as follows: "Mais l'attention fut surtout attireé par un animalcule de forme allongée et cylindrique. Les quatre cinquièmes antérieurs du corps avaient à peu pres la même diamètre. Le cinquième postérieur allait s'effilant de plus en plus et se terminait par une extrémité excessivement fine. Ce ver présentait des mouvements extrêmement vifs d'enroulement et de déroulement dans ses diverses parties et surtout dans son extrémité terminale." Demarquay's paper is accompanied by an admirable picture of the embryos.

The credit of the discovery is usually wrongly ascribed to Wucherer,[2] who, in Bahia, Brazil, in August, 1866, found embryos in the urine of a case of tropical chyluria. In 1868, Salisbury,[3] in the

United States, found the ova in the urine. Lewis,[4] in India, in 1872, discovered embryos in the blood of man, and noted that their presence was generally associated with chyluria and lymph scrotum. He proposed the name filaria sanguinis hominis.

Much of our knowledge of the life-history of the parasites is due to the really brilliant discoveries of Patrick Manson, whose scientific studies in this field have embraced a period of over twenty years. In 1878, Manson[5] discovered that the mosquito was the immediate host. This idea occurred almost simultaneously to Bancroft and Manson, but to the latter belongs the credit of demonstrating its truth. Manson found that the filaria embryos, ingested with the blood, develop in the stomach of the female mosquito. The mosquito seeks stagnant water in which to deposit her eggs; when death occurs the filariæ are liberated, and if the water be drunk they pass into the human body.

Lewis[6] confirmed Manson's discovery and described and depicted the development of the larvæ in mosquitoes. He showed that some of the filariæ pierced the walls of the mosquito's stomach and underwent developmental changes in the abdominal and thoracic tissues.

It was these observations upon the mosquito that led Manson[7] to suggest to Major Ross, in 1896, that it might also be the intermediate host of the malarial parasite.

Filarial periodicity was discovered by Manson.[8] He found that the embryos were present in the peripheral circulation only during the night. He believes this periodicity is an adaptation to the habits of the mosquito.

Mackenzie[9] showed that if the patient's habits were reversed, so that he slept by day and worked by night, the filarial migration was reversed. Mackenzie gives a chart of the filarial curve, showing the daily rise and fall most graphically. A blood examination was made every three hours, day and night, for a period of ten weeks.

Manson[10] has recently been able to demonstrate that filariæ when absent from the cutaneous circulation are lodged in the larger blood-vessels, especially of the lungs.

In addition to the well-known filaria sanguinis hominis of Lewis, there are a number of other species. Six have now been described. Manson[11] has named the original hæmatozoan of Lewis, filaria nocturna; the others he calls filaria diurna, filaria perstans, filaria Demarquaii, filaria Ozzardi, and filaria Magalhaesi.

The filaria nocturna and the filaria perstans are the only ones that are thought to be pathogenic. In 1891, Manson[12] found the embryo form of filaria perstans in the blood of a negro from the west coast of Africa. It observes no periodicity, being found in the peripheral circulation both day and night. It is much smaller than the filaria nocturna and differs somewhat in structure. The adult worm was discovered by Daniels[13] in British Guiana in 1898. Manson regards the filaria perstans as the possible cause of the sleeping sickness of the negroes of the west coast of Africa, and the skin disease craw-craw.

The most important of these parasites is the filaria nocturna. The adult form of this organism was not discovered until 1876. On December 21st of that year Bancroft, of Brisbane, Australia, found the female worm in a lymphatic abscess of the arm. In July, 1877, this fact was announced by Cobbold[14] in the *Lancet*. Cobbold named the parasite the filaria Bancrofti in honor of the discoverer.

Filariasis is widely distributed throughout tropical and subtropical countries. It occurs in a large part of China and India, in Japan, Australia, and the South Sea Islands. Thorpe[15] has shown that 32 per cent. of the inhabitants of the Friendly Islands are affected. Strube[16] found the embryos in the blood of negroes from the Transvaal. The disease occurs in Spain, and is very common in Brazil and the West India Islands. Guitéras,[17] in 1886, called attention to the existence of the disease in the Southern States. He found four cases in Key West and one in Charleston, S. C. De Saussure,[18] in 1890, published a report of twenty-two cases he had observed in Charleston. The city had been in constant communication with the West Indies, and doubtless the disease was introduced into this country from those islands.

Filariasis occurs particularly along the Gulf and South Atlantic coast. Many of the cases have been imported into this country, but in 1888, Mastin[19] reported an indigenous case in Mobile. De Saussure's twenty-two cases were of this nature. Slaughter[20] recorded, in 1891, two cases indigenous to the northern part of Virginia. Dunn[21] recently found the filaria embryos in a woman who had always lived in Pennsylvania.

So far as we know, the adult worms have never hitherto been found in this country.

Specimens of Adult Filaria Bancrofti Previously Found.

Bancroft, in a letter to Cobbold, dated from Brisbane, Queensland, April 20, 1877, said: "I have now obtained five specimens of the worm. . . . The worm is about the thickness of a human hair and is from three to four inches long. My first specimen I got on December 21, 1876, from a lymphatic abscess of the arm—this was dead. Four others I obtained alive from a hydrocele of the spermatic cord, having caught them in the eye of a peculiar trocar I use for tapping. These I kept alive for a day, and separated them from each other with great difficulty." The worms were preserved in glycerin and sent to Cobbold,[22] who described them. They were all females; only one of them was tolerably perfect.

On August 7, 1877, Lewis[23] found in a blood-clot from a lymph scrotum after a continuous search for eight hours, portions of a male and a female worm. The male worm was torn across in two places, and the terminal ends were missing, and the tail of the female could not be found. The male was twisted about a portion of the female and was separated only with difficulty.

On November 12, 1877, dos Santos,[24] in Brazil, found five adult females in a lymphatic abscess of the arm; only one worm was complete.*

In 1881, Manson,[8] in Amoy, China, opened an abscess of the thigh, and, by passing a needle rapidly through some dark, grumous clots that escaped with the pus, succeeded in finding three or four fragments of a female worm.

In the same year he found a female filaria in a dilated lymphatic in a case of lymph scrotum. On attempting to withdraw it the body snapped across. The specimen of lymph scrotum, with half the worm *in situ*, was shown at the London Pathological Society.

In 1888, Sibthorpe,[26] of Madras, India, found two worms, a male and female, upon the cut surface of a lymph scrotum. The specimens were studied by Bourne. The tail of the female was wanting. The male specimen was about an inch and a quarter long (3.1 cm.). The

* We doubt somewhat whether the filariæ which dos Santos found belonged to the species under consideration. His description does not conform with that of the filaria Bancrofti in all details. In deference to the opinion of such an authority as Cobbold,[25] however, we have included this case.

anterior extremity was not present. The male worm showed a great tendency to coil.

In 1894, Maitland,[27] of Madras, India, removed some thickened tissues from the inner surface of the left upper arm of a man who a short time before had suffered from lymphangitis in that region. Two operations were performed. The tissues removed were macerated in a mixture of nitric acid and chlorate of potash. In the lump first removed seven adult worms, and in the second, one were found. Three of these were males and five females. "Those first discovered were coiled up together in a mass, and appeared as if lying in a lymphatic channel, but owing to the maceration of the tissue it was difficult to be certain of this. . . . An interesting point in the case just related is the great number of the parasites that were found, and also the fact that they appeared to be all intimately associated with one another. So far as we know, such a large number of these parasites have never before been found in one individual, nor have they been found coiled together in one mass as a number of these were." Maitland mounted six of the worms in balsam and sent them to Manson who described and identified them. The tails of two of the females were missing, but the three males were complete.

Huber[28] states that Czerny found a living female filaria in the ovary of a woman from Rio de Janeiro. In 1897, Young,[29] in London, removed a hard, nodular mass from the arm of a young sailor, a native of Jamaica, who had lived in the West Indies, the United States, and Canada, who suffered from lymph scrotum and varicose groin glands. After several hours' examination of the tissue he noticed lying across his forefinger "a long white thread about the size of a horsehair." It proved to be a female filaria. Later the man committed suicide. An autopsy was performed. From a cut in a lymphatic of the right groin a small bundle was seen to emerge, looking like a tiny coil of very thin catgut. This was unravelled in normal saline solution and proved to consist of heads and part of the bodies of three female filaria Bancrofti. In the lymphatics of the right spermatic cord six more female worms were found, all more or less mutilated in the dissection. In the left spermatic cord seven worms were found. One of these was a male; it was an inch and a half long (3.75 cm.). It was in four pieces, and the tail was not discovered. Thus, in all, seventeen worms were obtained. Only one of these was a male.

In the case here reported nine worms were found in the lymphatics of the epididymis. Two of these were males. One of the males and one of the females were complete. The others were more or less mutilated.

Altogether we have collected eleven cases in which the adult filaria Bancrofti was discovered. In these cases fifty-one specimens of the worm have been found and studied. Forty-three were females; eight were males. The worms have rarely been found intact and complete.

Lewis, in 1877, was the first to discover the male. Both the tail and the head were missing in his specimen. Sibthorpe found the male again in 1888. The tail was present, but the head was gone. Maitland, in 1894, obtained three complete males. Young, in 1897, found a mutilated specimen. In our case two males were found, one of which was uninjured.

Location. The worms have been found three times in a lymph scrotum (Lewis, Manson, Sibthorpe). Once in hydrocele fluid (Bancroft). Once in the epididymis (case reported by the writers). Once in the ovary (Czerny). Once in the spermatic cord (Young). Four times in the arm (Bancroft, Maitland, Young, dos Santos). Once in the leg (Manson). Thus we see that in seven of the eleven cases the worms have been found in close relation to some part of the generative system.

In 1886, Magalhaes,[30] of Rio de Janeiro, found two adult worms, a male and female, in the left ventricle of the heart. He regarded them as filariæ Bancrofti. They are twice as long as the filaria Bancrofti, and differ in structure. Unfortunately, the description of Magalhaes filaria has crept into some of the best text-books of helminthology and medicine under the heading of the filaria Bancrofti.

Description of the Adult Worms. The male worm is shorter than the female. The intact specimen is shown in Plate III., Fig. 9, magnified ten times the natural size. The tail has a tendril-like twist, and the end is rounded and blunt. The worm is 3.86 cm. long; the body is 0.120 mm. in diameter; the head 0.051 mm.; the neck 0.043 mm.

The female measures between 7 and 9 cm. in length. The anterior extremity is tapering, but under the microscope the head is seen to be somewhat club-shaped. The mouth is unprovided with papillæ. A transverse section of the head and neck resembles somewhat the

shape of a Maltese cross. The diameter of the head is 0.068 mm. The diameter of the neck 0.051 mm. The diameter of the worm is greatest near the middle of the body, where it measures 0.240 mm. The surface is slightly irregular. During life transverse striations or corrugations were visible. These were probably caused by contractions of the subjacent muscular wall. The mouth is situated in the centre of the anterior end. The vagina opens near the head, the distance varying from 0.72 mm. to 1.3 mm. in different specimens. The anal orifice is near the tip of the tail, which is rounded and blunt.

The anatomy of the worm is best studied in serial sections. Portions of different worms were embedded in celloidin. Transverse sections were cut and stained with hæmatoxylin and eosin. The digestive tract passes down in the centre of the worm until the vagina is reached. The two tubes then run side by side. Lower down the greater part of the worm is occupied by the uterus, and the digestive tract is situated in the musculo-cutaneous wall. The vagina is 2.4 mm. long and has a thick, homogeneous wall. The uterus is composed of two thin-walled tubes which unite anteriorly. These tubes and the digestive canal are intertwined so that they have a braided appearance. The uterine tubes are of equal size, thin and structureless. The digestive tube appears about one-third the size of the uterine tubes in the fresh specimen, and presents a granular appearance. The uterine tubes are filled with ova and embryos in various stages of development. The ova average 0.035 mm. in size. The smaller embryos are coiled up and surrounded by a thin, structureless membrane—the chorion—and measure 0.050 to 0.060 mm. in their long diameter.

Manson[31] found that the females were brown, while the males were colorless. The specimens, however, upon which he based this statement had been removed from tissues macerated in a mixture of nitric acid and chlorate of potash and then mounted in Canada balsam. All our worms were white and opaque and resembled white threads. But we have noticed that when portions of the female worms were placed in impure alcohol, or salt solution, or became somewhat dried, that the walls of the uterine tubes assumed a brownish hue, giving the worms the appearance described by Manson.

Bourne,[32] and later Manson,[27] showed that the tail of the male is

provided with two spicules, which are retracted within the cloaca. In our complete worm, owing to the coiling of the tail, it was not possible to demonstrate the presence of these spicules without danger of mutilating the specimen.

Some authors lay stress upon the fact that the males show a great tendency to become coiled. This is doubtless true. But the female worms also may twist themselves into inextricable coils,

PATHOLOGICAL CHANGES IN THE TISSUES. Tissues were hardened in Zenker's fluid and in 10 per cent. formalin. The greater part of the wall of the thickened lymphatics is composed of muscle tissue. This is beautifully shown in preparations stained with Mallory's connective-tissue stain. The endothelium appears normal. Between it and the muscle tissue is a layer of connective tissue, and surrounding the groups of muscle bundles are large bands of connective tissue which pass from the intima to the adventitia. There are no areas of degeneration.

Sections stained with Weigert's elastic-tissue stain show many delicate elastic threads surrounding the muscle bundles. In the intima is a marked new formation of elastic tissue. The elastic fibres are arranged in loops extending from the media to the endothelium of the intima.

We have seen a similar process of muscular hypertrophy in the dilated and thickened veins of varicoceles. Soboroff,[33] many years ago, stated that he observed a constant hypertrophy of the muscle fibres of the media in varicose conditions of the veins. But the remarkable muscular hypertrophy that occurs in many cases of varicocele has received but little attention from recent writers. The new formation of elastic tissue in the walls of the lymphatics is analogous to that recently described by Janni[34] in varicose veins.

Although all parts of the testicle, epididymis, and spermatic cord were examined histologically, the adult worms were found only in the body of the epididymis.

Sections through the tissue upon which the mass of adult worms had been discovered showed portions of one or more female worms lying in large lymphatic spaces five to ten times the diameter of the worm. The small digestive tract and the larger uterine tubes are readily demonstrable. There are no signs of inflammatory reaction in the wall of the lymphatics that contain the worms.

In some of the lymph vessels are embryo filariæ. Throughout the fibrous tissue between the lymphatics are numerous foci of lymphoid cells. It is interesting to note in this connection that Dr. Steensland found an increase in the number of small lymphocytes in each of the three differential blood-counts that he made.

One large lymph vessel is almost completely obliterated by a mass of granulation tissue, in the interior of which are apparently two portions of an encysted necrotic worm. With the exception of a clear zone immediately around the worm the ingrowth is densely infiltrated with lymphoid cells and eosinophiles.

A search of the literature reveals only one case in which an adult filaria has been found in the tissues on histological examination. Marie[35] discovered a dead female worm in an inguinal lymph node removed from a man affected with filariasis. The worm was surrounded by pseudotuberculous tissue.

Our observation explains one method by which the large lymphatic vessels may be occluded and lymph stasis produced. A worm dies and gives rise to a thrombus, which, as a rule, probably only partially blocks the vessel, as the lumina of the dilated lymphatics are many times the diameter of the worm. Later a growth of connective tissue extends from the wall of the vessel into the lumen. It surrounds the dead worm and obliterates the lymph channel.

It is not at all impossible that the lymph stasis may also be produced in other ways. Manson found ova in a lymph node. These he assumed were discharged prematurely from an adult worm, and having a larger diameter than the embryos they would block the minute branches into which the afferent lymphatics break up in the lymph node.

It is known that the worms may live for many years in the body. Our patient left the West Indies four years before the time of operation. Hence, the live adult worms were at least four years old.

Description of the Filaria Embryos. The embryos measure 0.260 to 0.300 mm. in length, and 0.006 to 0.008 mm. in breadth. Their anterior end is rounded. Their tail is pointed. It is enclosed in a thin, transparent sheath which is much longer than the worm. Rarely the filaria can be seen moving forward and backward within its sheath. The collapsed sheath extending beyond the head often appears like a single waving cilium lashing the red blood-corpuscles

at some distance, 0.030 to 0.040 mm., in advance of the head. The embryos are in constant motion, writhing, coiling and uncoiling, but they never exhibit a true progressive movement.

In the hydrocele fluid many empty sheaths were found after it had stood in the laboratory forty-eight hours. Manson[36] produced this ecdysis by cooling blood which contained filariæ nearly to the freezing-point. The embryos have remained alive as long as five days in a cover-slip preparation of the blood kept at room temperature. They seem to undergo a granular degeneration. Henry[37] states that he has kept them alive in a cool room for ten days. In the thermostat at 37.5° C. they usually die in two or three days. When the lashing movements of the body had nearly ceased a peculiar "pouting" movement of the head was observed. Whether this was due to the protrusion of a proboscis or the retraction of a prepuce-like structure, as Manson[38] maintains, we were not able to determine. Attached to the tip of the head is a tiny spine. The pouting movement was found to be repeated twenty-eight to thirty times in a minute.

The structure of the embryos was best studied by fixing ordinary cover-slip preparations of the blood by heat or by a saturated solution of corrosive sublimate, as recommended by Plehn,[39] and staining for a few seconds with Löffler's methylene-blue or with a 2 per cent. solution of thionin. When stained the body is found to be studded with irregular, deeply-staining granules. Near the junction of the middle and posterior thirds of the body is an elongated homogeneous structure of wavy outline. Sometimes it is plainly visible in living embryos. Sometimes no trace of it can be seen.

Flint[40] has advocated methylene-blue in the treatment of filariasis, while Laveran and others have recommended quinine.

The following experiments were tried with the hydrocele fluid: A drop of hydrocele fluid was mixed with a drop of 1 : 1000 methylene-blue solution. The filariæ were actively motile after two hours. A drop of quinine sulphate solution 1 : 1000 was mixed with a drop of hydrocele fluid. Some filariæ became motionless within a few seconds; all within three minutes. These results agree with those obtained by Laveran.[41]

Neither of our patients was anæmic. The red count in Case I. was about 5,000,000. Lazarus[42] in his recent work states that filariasis is the cause of severe anæmia. Doubtless the complications, hæmato-

chyluria, chylous diarrhœa, etc., may produce this condition, but the filaria embryos *per se* do not appear to impoverish the blood at all.

CLINICAL CONDITIONS PRODUCED BY THE PRESENCE OF FILARIA NOCTURNA. (The other varieties of filariæ will not be considered in the following pages.)

The presence of filaria embryos in the blood or other fluids of the body is proof of the existence of live parent worms whose habitat is in some portion of the lymphatic system. The duration of life of the parent worm is unknown, hence it has not been determined how long a person may remain a victim of filariasis. Even if the adult worms should die the patient is liable to be reinfected in tropical districts. It is very common for inhabitants of the tropics to harbor the filaria nocturna and yet show no symptoms that would lead one to suspect its presence.

There is no evidence which shows that the parent worms live in other than the lymphatic vessels, or that they migrate from one part of the body to another. The very meagre evidence showing that a subject ever gets rid of the embryos when once infected points to the fact that the parent worms are multiple and abide in different locations. We can find no authentic cases where the embryos have disappeared after the removal of parent worms, which demonstrates that others still remain, although such removal is very frequently followed by complete and permanent relief from all symptoms. Hence, one may be a victim of filariasis and yet not suffer any inconvenience.

So far as known, the embryos do not cause any pathological changes, for their small size enables them to be carried freely throughout the circulatory system.

The parent worms, on the other hand, are capable of producing many different clinical manifestations, consequent, primarily, on obstruction to the lymph circulation. This obstruction is rarely due directly to the worm, but is generally the result of secondary changes which thicken the walls of the lymphatics, and thus narrow their lumen.

Furthermore, the location of the parent worm is frequently the seat of infection, and the presence of an abscess or lymphangitis may be the first warning of any trouble whatever. Manson suggests that the ova are capable of obstructing the smaller lymphatics, and thus he accounts for certain pathological changes.

Hence, the clinical manifestations depend upon lymphatic obstruction, complicated or not by secondary infection.

The symptoms may be:

1. General or constitutional.

2. Local, thus open to wide variations according to the part involved, whether as the result of stasis alone or modified by infective processes.

CONSTITUTIONAL SYMPTOMS. The first warning of the presence of filariæ is often given by the more or less sudden onset of constitutional symptoms before any local signs appear. General debility and fatigue after exertion, and irregular periodical febrile attacks somewhat resembling malaria, are common early symptoms. Pain in the back, pelvis, and groins is frequent, and it may be very acute and accompanied by nausea and vomiting. These attacks are generally relieved by absolute rest, and produced by exertion. Their increasing frequency, together with the appearance of local signs, particularly about the genitals, may be accompanied by severe mental depression, melancholy and sexual neurasthenia.

When a local area becomes infected with pyogenic organisms the usual constitutional disturbances follow.

In certain mild cases, without local signs, where filariæ have been discovered in the blood, an occasional slight transitory febrile attack is the only evidence of filarial disease. In other instances the presence of embryos in the blood is the only evidence that apparently perfectly healthy individuals are subject to filariasis.

LOCAL MANIFESTATIONS. Local signs consequent on the presence of filariæ are subject to great variation according to the part affected. They are due primarily to obstruction of the lymphatic circulation, thus causing injury, and secondarily to the invasion of pyogenic organisms. The changes due to obstruction progress slowly.

Filaria nocturna is known to produce the following local pathological changes:

(1) Dilated lymph glands—varicose glands. (2) Dilated lymph vessels—lymphangiectasis, lymphatic varix. (3) Probable rupture of dilated varices, giving rise to chyluria, chylous hydrocele (chylocele), and rarely chylous ascites and chylous diarrhœa. (4) Cutaneous lymphatic obstruction manifested as œdema—lymph scrotum, lymph vulva, and probably elephantiasis Arabum of the tropics (Man-

son). (5) Results following pyogenic infection—cutaneous lesions, lymphangitis, cellulitis, abscess. (6) Two or more of these conditions may be associated in the same individual.

1. *Dilated Lymph Glands.* This condition is generally associated with dilated lymph vessels running to and from the glands. The glands of the groin are by far most commonly affected, and either the inguinal, femoral, or both may be involved. It is unusual to observe changes in other lymphatic glands.

They increase slowly, and, as a rule, there are no subjective symptoms to attract the attention of the patient until they have attained considerable size. Then there is a feeling of tension and weight. Unless they are inflamed the skin over them is normal and freely movable. The glands themselves are soft, compressible, doughy and ill-defined, and not ordinarily tender. They decrease in size when patient is lying down, and slowly refill when he is erect. The collection of glands may be as large as the fist.

There should be no difficulty in differentiating them from herniæ, varicocele and varicose saphenous veins. They may be aspirated safely, and the fluid will be yellow, white, or reddish, according to circumstances, and will generally contain embryos. The glands themselves consist of a dilated meshwork containing channels or cavities filled with lymph. Infection with pyogenic organisms gives rise to adenitis and peri-adenitis, which may result in abscess formation.

2. *Dilated Lymph Vessels* (*Lymphangiectasis*). There are occasionally to be seen on the surface of the skin minute lymphatic dilatations. These may suddenly disappear or they may rupture and allow the escape of lymph. The larger lymphatic trunks under the skin are usually associated with dilated lymph glands. The case here reported would seem to be somewhat unusual, for the glands of the groin were normal, but the lymphatics of the cord were much dilated and thickened, as described above. The lower end of these lymphatic trunks was continuous with the lymphatic dilatations in the testis. In all probability there are points of obstruction in the pelvic lymphatics of this case, which condition alone would seem to account for the dilatation throughout the cord. Clinically the condition resembled that of varicocele.

When infected, a lymphangitis results which is manifested by the usual red streak and indurated cord and the ordinary constitutional

reaction. Infection of the cutaneous lymphatics is common in lymph scrotum and elephantiasis.

3. *Rupture of Dilated Varices.* (*a*) Chyluria. This is one of the commonest signs of the presence of filariasis. It may be of sudden onset, and be the first warning of any trouble, or it may be preceded by obscure pains in the lower abdomen and pelvis. Although its appearance is of comparatively sudden origin, it is the result of a chronic process, which has probably existed for months and even years. It is probably the commonest external manifestation of the presence of filariasis, and it is less apt to be associated with other varieties of external changes.

It is probably due to the rupture of dilated varices into some portion of the urinary tract, either the bladder or the kidney. Autopsies on such patients show that the abdominal and pelvic lymphatics may be enormously dilated, thereby obscuring some of the retroperitoneal structures. As a result of such ruptures the contents of the lymphatics is poured into the urinary tract, so that the voided urine contains its normal constituents unaltered in addition to the lymph. The appearance of the urine will vary according to the character of the lymph, but it is generally turbid. It is apt to be milky-white soon after the process of digestion has commenced on account of the excess of fat, but later it is paler on account of the more serous character of the lymph. The urine may become clear suddenly, or remain chylous for weeks and months, then become normal, and remain so permanently, but the chyluria is more apt to recur at some later period. Lanceraux[43] records a case where it persisted fifty years.

In addition to the unaltered normal constituents, the urine contains the products of the lymphatics. It is uniformly turbid when voided, but soon separates into three more or less distinct layers. The great bulk of the urine remains rather uniformly turbid on account of the divided fat globules, but on the surface is a yellowish layer due to larger collections of fat, and on the bottom of the glass are clots of fibrin often discolored with red blood-corpuscles. Hemorrhage is so striking in some cases that the condition is often called hæmatochyluria. These clots not infrequently form in the bladder and cause temporary obstruction. The urine becomes clarified when shaken with ether. The microscope may show the presence of active embryos.

Although chyluria is the result of a very chronic process, there are certain recognized exciting influences which cause the dilated lymphatics to rupture. Thus chyluria may appear in women after parturition and in men after violent exercise. Like all inaccessible varices, these must be left to take their course.

Chyluria is not directly dangerous to life, but an excessive loss of chyle may cause debility and worry on the part of the patient, may result in mental depression so as to incapacitate him for all sorts of active work. The obscure pains in the back and pelvis are probably due to the over-distended lymphatics.

(*b*) Chylous hydrocele. This complication is the result of obstruction of lymphatics, so that the chyle is poured into the tunica vaginalis testis. In the case which is here reported the "chylocele" appeared for the first time after the primary operation at which the dilated lymphatics of the cord were excised. This prevented the normal return of the lymph from the testis which was provided for by these dilated channels in spite of partial obstruction of the lymph current. The accumulation began at once after these vessels were ligated. The presence of numerous parent worms in the vicinity of the testis was undoubtedly the cause of this excessive escape of lymph, for this operation was practically the one employed in the radical cure of varicocele, which is not often followed by an acute hydrocele.

The physical signs of chylous hydrocele do not differ from those of an ordinary hydrocele. So far as we could determine, the translucency was nearly as pronounced. Knowing what we did in reference to this case, the cause of the fluid accumulation was obvious, but under other circumstances, aspiration and microscopical examination will determine the condition. The character of the fluid in chylous hydrocele has already been described.

The association of a scrotal tumor with varicose lymph glands or other varices should make one suspicious as to its nature. In patients who have visited the tropics any turbid hydrocele fluid should be subjected to microscopical examination in order to determine the diagnosis.

In cases of chylous hydrocele it is probable that parent worms are present in the vicinity of the testis, and on more than one occasion these worms have been recovered from the fluid. Our case demon-

strates the value of radical interference. In sixty-two cases of filariasis reported by Manson there were six cases of "chylocele."

These cases may become infected and manifest the usual signs. A lymph scrotum is not an unusual sequence if they are left to take their course.

(*c*) Chylous ascites is probably a frequent complication where the abdominal lymphatics are involved, although there is but little evidence, clinical or pathological, to confirm this statement. The peritoneum would probably absorb the escaped lymph, and no harm result. In the tropics the presence of turbid fluid, which could not otherwise be accounted for, should make the surgeon suspicious as to its character.

(*d*) Chylous diarrhœa is a rare complication.

4. *Cutaneous Lymphatic Obstruction.* (*a*) Lymph scrotum is the result of obstruction in the lymphatics of the integument, and is usually accompanied by other external signs, most commonly by dilated lymph glands. The skin of the scrotum is permanently thickened, but its surface remains intact for a period at least. Vesicles and small varices may appear on the surface, and these may rupture later and allow the escape of lymph. Its color will vary according to circumstances, and the amount may be considerable. Inflammatory changes generally follow, and thus the surface of the scrotum may become eczematous and ulcerated, or cellulitis and abscess may appear in the deeper layers. Thus the scrotum becomes permanently enlarged and resembles true elephantiasis.

(*b*) The changes in lymph vulva are analogous to those in lymph scrotum.

(*c*) Elephantiasis Arabum (tropics).

It is still a disputed question as to whether this condition is a manifestation of filariasis, but Manson offers many convincing arguments in support of this theory. If such is the case, then elephantiasis is the commonest manifestation of the presence of filaria. This question will not be considered here.

5. Results following pyogenic infection: Cutaneous lesions, lymphangitis, cellulitis, abscess.

Many of these conditions have been considered.

It is not unusual, however, for a patient to present himself for treatment on account of an attack of lymphangitis or abscess, more

particularly on the extremities. There is often the history of a trauma.

Adult worms have been found in these lymphatic abscesses, after the removal of which local recovery follows, but in no case, so far as we can learn, have the embryos permanently disappeared from the blood, showing that parent worms have always existed elsewhere.

Ordinarily a dead worm probably becomes encysted, as demonstrated in our case, but if infection should take place, lymphangitis or abscess is the usual course, and the dead worm may be discovered in the pus. These local signs of infection may be the only external evidence of anything wrong with the patient, but an examination of the blood may reveal the presence of the embryos.

6. That two or more of the above conditions may be associated in the same individual, accompanied or not by secondary inflammatory changes, need not further be discussed.

Course and Prognosis. Cases of spontaneous recovery are recorded. There are no recorded cases, so far as we know, where operation has been followed by the permanent absence of embryos, although it is common for such patients to be permanently relieved of further objective and subjective symptoms. The length of life common to the parent worm has not been established, but if the patients should not be exposed to later invasion, in all probability the parent worms would die in time and no further embryos appear. Much of the damage, however, sustained by the lymphatics can never be repaired. Most of the cases which have been studied thus far have continued to dwell in the tropics and are thus exposed to secondary invasion.

In many cases the parent worms reside in inaccessible lymphatics, and therefore cannot be reached, and the case must be left to take its course. In other instances the parent worms are accessible to the surgeon, and their removal is often followed by great benefit and sometimes apparent recovery, as in our case, although a few embryos still exist, showing that he still harbors more parental forms. In all probability the number of embryos present is a fair guide as to the number of parent females. The embryos may be too few to be detected by casual examination. Many subjects of filariasis escape without any symptoms, and the embryos themselves do no harm so far as is known.

Filariasis, when due to the filaria nocturna, runs a chronic course

and is not a direct danger to life. Fatal issues have generally followed some intercurrent infection.

Certain local manifestations can be permanently relieved by surgical measures.

PROPHYLAXIS. Filariasis cannot be transmitted directly from one person to another, for the embryos require an intermediary host before they can develop into adult worms. It seems to have been demonstrated beyond question that certain species of mosquito act as this host, and that the young filariæ continue their existence in water, and are thus taken into the system.

In filarial districts all sources of drinking water should be protected from mosquitoes. Cisterns and wells should be kept covered. The only safe precaution is that all drinking-water should be either filtered or boiled, and at some future time the filtration of the municipal water-supply may be demanded. Reservoirs should be cleaned often and regularly. It is never safe in such districts to drink from open streams and pools.

Our patient states that it is customary for the white population of Barbadoes to drink only filtered water, but that he and his brother were in the habit of drinking from any pool while on hunting trips.

In a moderate degree subjects of filariasis are a danger to a community.

TREATMENT. Where the presence of embryos alone is the only sign of filariasis no treatment is necessarily called for in order to relieve any symptoms, but, furthermore, there is no known method whereby such embryos may be removed. On the other hand, the embryos *per se* are harmless so far as is known. All treatment, therefore, to be of any permanent value, must be directed toward removal of as many of the parent worms as possible. In that the lymphatics most commonly involved (pelvic and abdominal) are not readily accessible, and the exact location of the parasites is difficult to determine, these cases are best treated by allowing them to take their course. But if secondary complications follow, then surgical measures may be of great service.

MEDICINAL TREATMENT. There are at present no known drugs, when administered to the patient, which have proved to be of value in killing the adult worms. It is the custom in filarial districts to administer large doses of quinine. Although weak solutions of this

drug will kill the embryos outside of the body, its administration seems to have no effect on them in the circulation, and their persistence shows that it is not capable of killing the adults. Its use, however, is probably of value in counteracting some of the secondary constitutional symptoms.

It is not improbable that local injections of certain antiseptics might serve to kill the parent worms if they could be located. Even then only certain regions would be accessible to such treatment.

Operative Treatment. As a general rule, operative treatment is of value only in relieving certain local conditions. If the site of such local condition should happen to be accessible to the surgeon, and to be the only nidus of adult worms, then operation might be curative; but, unfortunately, this must be a rare circumstance. These facts do not contraindicate operation.

The immediate indication for operation is generally some local result of lymphatic obstruction, complicated or not by secondary infection. During the dissection of these wounds there may be considerable escape of lymph, so that it is wise to ligate all lymphatic vessels carefully. The oozing of lymph can otherwise be controlled by packing and pressure. Such wounds generally heal in the ordinary manner. Local recurrences are unusual.

Treatment of and Operations for Special Complications.

1. *Dilated Lymph Glands.* These glands are usually part of a large varix, and if they are small and do not cause any inconvenience, it is wise not to interfere. If they are large enough to cause discomfort, or if they are the seat of recurring inflammatory processes, it is advisable to excise them.

Such excisions have been followed by chyluria and elephantiasis of the leg, but this does not necessarily prove that these are direct results.

2. *Lymphangiectasis.* Dilated lymph varices are usually associated with other neighboring complications and should be treated simultaneously. Dissection should be as complete as possible and both ends of large vessels ligated.

3. *Chyluria* is considered to be the result of rupture of varices which are practically inaccessible, so that such cases are not suitable

for operation. The patient should be put to bed and the hips elevated in order to reduce the hydrostatic pressure. The diet should be restricted, and the fat elements withheld so far as possible. Cathartics and diuretics are valuable in order to relieve the tension in the lymphatics, and thus allow the rupture to close. Otherwise the case must be left to take its course.

4. *Chylous hydrocele* is simply a collection of lymph in the tunica vaginalis testis. In our case many parent worms were lodged in the testis and at the same time the lymphatics of the cords were much distended, and thus extended into the abdominal cavity, showing that pelvic obstruction must exist.

In such a case simple incision or the injection of irritants would not cure a hydrocele, nor would it be practicable to attempt to dissect out adult worms from the lymphatics about the testis. Operation must be radical, and it would seem to be wisest to excise the testis and the cord as high as possible. In this case the local cure was prompt, uncomplicated, and thus far it has remained permanent.

The rare complication of chylous diarrhœa should be treated by rest and on general principles.

Chylous ascites would probably be recognized only in the course of a cœliotomy for some intercurrent cause.

5. *Lymph Scrotum.* The scrotum should be kept scrupulously clean and dry; it should be powdered, protected, and suspended. By this means infection may be avoided for a time. When its size makes it troublesome, or if it is the seat of recurring attacks of inflammation, then it should be excised. Margins of healthy skin should be left and the testicles need not be sacrificed. Flaps of skin may be obtained from the thighs, if necessary, to cover in the wound.

6. *Elephantiasis* is a condition which is permanent and tends to increase. Ninety-five per cent. of the cases involve the leg. In the early stages the process may be retarded by the use of elastic bandages, careful massage, and resting the part as much as possible. Its progress is usually slow unless the surface becomes excoriated and infected, when secondary symptoms and changes set in. In the tropics the part should be protected from the hot sun, and the leg should be kept dry. Occasionally excision of strips of skin may be of palliative value, but at times the condition of the leg may be such that only

amputation will give relief. Most cases of elephantiasis are troublesome on account of the secondary inflammatory processes.

Elephantiasis of the scrotum may follow a lymph scrotum and reach enormous dimensions. Removal by operation is the only method of relief, and this may be performed with comparative safety.

Elephantiasis elsewhere has been rarely subjected to surgical intervention.

7. *Infective Complications Associated with Local Filarial Lesions.* These complications are very common and may be manifested as erysipelas, lymphangitis, cellulitis, and abscess. Constitutional symptoms, often severe, are present at one time or another. The ordinary methods of treating infected wounds should be made use of according to circumstances. After the acute process has subsided the various local lesions may be treated in a radical manner as described above.

Comparatively few operations have been performed for filarial processes, and most of these have been carried out in the tropics, notably at the Madras Hospital, India, where many of the results have been excellent.

We take this opportunity of expressing our thanks to Dr. Councilman and to Dr. Mallory for advice and assistance; to Messrs. Brinckerhoff and Richardson, of the Harvard Medical School, for the excellent photographs, and to Miss Jones and Dr. Howe for the drawings.

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REPORT OF A CASE OF ACUTE GRAVES' DISEASE WITHOUT EXOPHTHALMIC GOITRE.

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The following case is deemed worthy of record, in connection with the paper by Dr. Thomson, because of certain special interesting features:

E. S., male, Hebrew, clerk, aged twenty-four years. On February 14th and 15th he was cited to appear as a witness in a case at court. The court-room was overheated. Many present complained of this, and E. S., who was warmly clad and suffered from the undue heat, at the expiration of five hours, as the court was about to adjourn, rather suddenly broke into a profuse perspiration. This continued unchecked after he reached his home toward evening, so that his underwear and linen were noticed to be extremely wet. Sweating persisted through the night, though to a less degree, and on the following day, which he had again to spend in court, it was profuse. Toward the end of the second day spells of "shivering" appeared, and on the third day he was compelled to keep his bed. A few days subsequently I was asked to see him by Dr. Albert Bernheim, his attendant. During this time it was reported that sweating had continued unabated, so that his body and bed-linen had to be frequently changed. This free perspiration had been so marked a symptom as to almost overshadow others that had appeared. There was noticed to be a constant fine tremor in the hands, facial muscles, and in the tongue on its protrusion, and spells of coarse tremor involving all the voluntary muscles of the trunk, extremities, and jaws, occurred at intervals. There was considerable flatulent distention of the abdomen and the presence of borborygmi. The heart was rapid, but free from murmur; the pulse in recumbency ranged between 100 and 120, and was of low tension. The hands were somewhat swollen and the palms intensely red, as if dyed with eosin. The general bodily surface was wet with perspiration, and the entire trunk was covered with miliaria. The eyes were not prominent, nor have they since become so, and von Graefe's and Stelwag's signs were not present, and have continued absent. The thyroid was not palpably swollen and the goitre has not since appeared. The patient was debilitated, irritable, and sleepless. The urine contained a small amount

of albumin, but no glucose. There were cylindroids and a few narrow hyaline casts. The patient is of robust build and of good habits. He had been in previous good health, and had never before had an illness which confined him to bed. Dr. Bernheim, who is intimately acquainted with his family and their history on both sides, asserts that both are free from neurotic tendencies, and that the patient, under his observation from childhood, had never exhibited any indication of either organic or functional nervous ailment, and could not be regarded as of an emotional nature or hysterical; but, on the contrary, he asserts, had always seemed very virile physically and mentally.

Atropine, digitalis, and strychnine were prescribed, and at three-hourly intervals a cold shower of several minutes' duration, with a fine spray producer, during which energetic friction of the extremities and trunk was practised. The immediate results were good. He perspired very little, unless too warmly covered, and the spells of coarse tremor were less frequent and violent. The baths, which he took readily and looked forward to with pleasure, because of their marked bracing effect, were efficient in temporarily controlling certain of the symptoms, such as the tremors and sweats, and in imparting a feeling of well-being. Three weeks from the onset of the ailment, after considerable improvement had occurred, he was informed of a fire at the business place where he had been employed. Immediately after this his pulse, which Dr. Bernheim had reported had not, in recumbency, exceeded 90 for some days, rose to 160, and sweating, such as had existed with the onset of his ailment, re-began, so that it was said in about fifteen minutes his night-dress required changing, because it had become so thoroughly wet. The spells of coarse tremor now reappeared, and he again became greatly debilitated. The general shower was returned to and hyoscyamine combined with strychnine, and, after a few days, for the tachycardia, which persisted, galvanization of the cervical sympathetic, after the method of Cardew, was instituted. This last, which I have used with great benefit for its influence on the rapid heart in other cases of exophthalmic goitre, here was of undoubted value. A current of two or three milliampères was employed three times daily for five minutes, the anode (three inches in diameter) to the suboccipital region and the cathode (one and a half inches in diameter) to the anterior edge of the sternomastoid clavicular attachment.

On April 1st the patient was sent to Atlantic City, where he has since remained. The use of galvanism had then to be discontinued. He has lately been taking full doses of suprarenal extract, in addition to strychnine, atropine, or hyoscyamine. The heart continues overactive and the blood-pressure low; the skin leaky, and fine tremor persists. He is still unable to resume his occupation, although about. Prominence of the thyroid or of the eyes has not developed.

This case is evidently one of severe, acutely arising vasomotor disorder of the nature of Graves' disease, occurring in a previously healthy

male adult, in whose family there is no history of organic or functional nervous disorder. Other evident cause lacking, the disease presumably originated by nervous strain incident to spending two days in court, to which he was summoned as a witness in a case which was said to be of no actual importance to himself.

The temperature of the court-room had been somewhat excessive through the day, and the patient, as before remarked, had suffered in consequence. The profuse perspiration was the first manifest sign of the ailment. This was accompanied, or immediately succeeded, by marked suffusion of the body and extremities, rapid heart-action, fine tremor, and, on the third day, paroxysms of coarse tremor, and by marked flatulent distention of the abdomen; by prostration of strength, mental irritability, and by insomnia. Dr. Bernheim, who was in constant attendance in the capacity of nurse as well as physician, states that the amount of sweat exuded during the first week, before this symptom had been controlled by atropine and by hydropathic measures, was really extraordinary. The patient, previously robust, of cheerful disposition, rapidly became physically debilitated, irritable, and depressed. Despite the sudden onset of symptoms, with profuse and continuous exhausting sweats, and, in a day or so, tremors, rapid heart and other symptoms undoubtedly establishing the existence of acute Graves' disease—enlargement of the thyroid and prominence of the eyes have remained absent to the present, at which time considerable amelioration of the symptoms is evident. Although it is common for rapid heart to precede by weeks or months the development of struma and exophthalmos in cases of Graves' disease usually seen—those of deliberate onset—it is unusual in a case so acute and so severe as this. Here sweating, tremors, and tachycardia became the prominent triad in place of tachycardia, swollen thyroid, and exophthalmos.

Dr. Bernheim had a previous intimate acquaintance with the patient from babyhood, and as intimately knew both branches of his family and their histories. He was, from immediate personal observation, enabled to positively state that no symptoms of the ailment had previously existed—neither rapid heart, nor leaky skin, nor tremors, nor the other minor ones narrated—that, on the contrary, the patient was physically robust and mentally virile, and both paternal and maternal side were free from recognizable neuropathic taint. There is little doubt

that the presumed cause mentioned originated the ailment, and that although the patient, as he alleges, was unaware of it, sufficient peculiar nervous strain accompanied the attendance at court, in anticipation of appearing as a witness, though in a trivial case, and concerning which a verdict for either side should not have actually affected him, to induce a condition of vasomotor upset, continuing as true Graves' disease. The excessive temperature of the court-room, in which on the two successive days he spent five hours each, and from which he early suffered on the first day, was doubtless also a factor in the induction of the sudden vasomotor derangement. Excessive heart-action was not remarked until the third day after the development of the profuse perspiration, although it probably originated coincident with the latter, its onset being at first completely overshadowed. That nervous though unconscious dread had been the chief factor was shown by the fact that, as remarked in the history in the third week of the ailment, and after a decided improvement had occurred, on his being told that the business place at which he was employed had just been partially detroyed by fire, rapid heart (160 in recumbency), profuse sweatings, and tremors again became prominent, and the patient lapsed into a condition of debility, which had previously been so manifest.

It is interesting that the patient is a Hebrew of German parentage. It is, I believe, a fact that the Polish, Russian, and German Jews are regarded to have an especially mobile nervous organization, the derangement of which is more easily accomplished by causes which are less readily operable in the Jew of other nationalities and in the Aryan race.

A REPORT OF CASES OF PERNICIOUS ANÆMIA, WITH SPECIAL REFERENCE TO THE BLOOD FINDINGS.

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Of the twenty cases herein reported the diagnosis of pernicious anæmia was based upon the clinical history and the physical findings, but most of all upon the blood condition. The individual histories, briefly given, show in most of the cases the absence of morbid physical findings, except those due to anæmia. The noteworthy anatomical changes recognized clinically are noted in the general conclusions. The high color index, the severe degree of poikilocytosis, the constant presence of polychromatophilia, and the presence of megaloblasts, usually predominating at some period of the observation over the normoblasts, were considered pathognomonic of the disease. In five of the cases but one personal examination of the blood was made. The history of these cases and the blood find was so characteristic that it seems proper to report them as pernicious anæmia. In all the remaining cases a sufficient number of observations were made and the cases were studied over a sufficiently long period of time to make the diagnosis certain. Six of the cases were observed and studied over a period of from five months to one year. In most of these cases blood examinations were made every month. The clinical course was found to be that usually observed. Periods of improvement occurred, followed by periods of decline. During these periods the blood condition was materially altered. Charts of the blood condition, showing the color index, the number of red and white cells, the percentage of hæmoglobin and the number of nucleated red cells per cubic millimetre of Cases X., XI., XIII., XIV., and XV., during periods of improvement and decline, show more emphatically than words the varying conditions of the blood.

Chart No. VI. shows a differentiation of the white cells in Case XV. It will be noted that in most of the cases the white count is decreased and the number present corresponds somewhat with the rise and fall of the red cells and percentage of hæmoglobin. It will also be noted that the decrease in leucocytes is due to an absolute decrease in the polymorphonuclear forms.

The accompanying table of the blood counts, including the differentiation of the white cells, the enumeration of the nucleated red cells, the presence or absence of degeneration of the nucleus of the megaloblasts (classed as irregularity of the nucleus), the presence or absence of poikilocytosis and polychromatophilia (+ = marked, + + = very marked, + + + = extremely marked) is self-explanatory. In the table and charts the percentage of hæmoglobin is based upon the estimation made with the Fleischl instrument, and the actual reading is given uncorrected. In estimating the color index the usual correction of the Fleischl reading was made by adding 10 per cent. The Thoma-Zeiss instrument was used for all blood counts.

Of the twenty cases ten have died. Upon two only was it possible to obtain an autopsy. In both the post-mortem findings were typical of the disease. As nothing unusual was found, I shall not take space to describe the morbid anatomy. In the other eight cases autopsy was not made because of objections made by relatives or because the patient was at some distance in the country and inaccessible to the writer at the time of death.

CASE I.—Male, aged sixty-two years, admitted to the Cook County Hospital March 18, 1899. Laborer, suffering from great weakness, prostration, and profound anæmia. Physical examination revealed general arterio-sclerosis, emphysema pulmonum, with dilatation of both sides of the heart.

Blood examination showed 1,400,000 reds, 24 per cent. hæmoglobin, and 21,000 white cells. There was present marked poikilocytosis, polychromatophilia, and a total of 168 nucleated red cells per cubic millimetre, of which 84 were megaloblasts. The patient died on March 20th. No autopsy was obtainable.

The physical findings in this patient were senile in character, and there was nothing to account for the conditions of the blood in the physical findings.

In this case the color index was below normal. The leucocytosis was probably of the terminal form, as the patient died two days later. This accounts for the excess of the polymorphonuclear neutrophiles which were present. The megaloblasts were typical and showed much irregularity of the nucleus.

CASE II.—Female, aged thirty-four years, married, American, and has

borne one child. Was first seen in May, 1898. She gave a history of illness of about one year's duration. She was pale; complained of want of strength and endurance.

Blood examination revealed 2,800,000 red cells and 40 per cent. of hæmoglobin. There were no nucleated red cells found, and the white count showed 8000 per cubic millimetre. The spleen was palpable. There was a slight eczema-like eruption in both axillæ and about the pubic region. The urine was of light weight, but contained no abnormal ingredients.

The physical findings were negative except those named. The patient improved upon restorative treatment of arsenic and iron. In the fall of 1898 she complained of weakness of the lower extremities associated with paræsthesia. There was tenderness upon pressure over the anterior crural nerve and over the musculo-cutaneous branch of the external popliteal. The knee-jerk was diminished. The patient had good control of the bladder and the bowels. The anæmia was still present and practically of the same grade as at the first examination. The patient was not seen again until August, 1899, when she presented evidences of paraplegia associated with paræsthesia of the skin of the lower extremities, diminution of tactile, temperature and pain sense, a partial loss of control of the bladder, marked ataxia, and incoordination. The knee-jerk was entirely lost; the Argyll-Robertson pupil was not present; the fundi were normal. The pulse was rapid—90 to 100 per minute—and the temperature subfebrile, usually normal in the morning, but from 99° to 100° in the evening. From the middle of August the patient grew worse, with rapidly diminished power in the lower extremities, until complete paralysis resulted, with loss of control of both the bladder and the bowels. Tympanites was constant, the anæmia increased, and on August 31st a blood count showed 34 per cent. of hæmoglobin, 1,010,000 red cells, and 6000 whites, with 228 nucleated cells per cubic millimetre, of which 189 were megaloblasts. Poikilocytosis was marked and polychromatophilia present. The paralysis extended upward, involving the successive segments of the cord with corresponding nerves, and the patient finally died on September 7, 1899, from involvement of the respiratory and cardiac centres.

This patient at the beginning showed anæmia which did not present the characteristics of a pernicious anæmia, either in the color index or in the presence of nucleated or irregular-sized and formed cells. Later, the spinal cord symptoms predominated, and although the anæmia was observed and was considered important, it was not looked upon as a pernicious type until the final examination, eight days before death. The character of the blood at this time was so characteristic of pernicious anæmia that one is forced to look upon the case as primarily a pernicious anæmia with the spinal cord lesion as one of the not unusual accompaniments of the disease. An autopsy was unobtainable.

The blood findings in this case were typical of pernicious anæmia. The megaloblast, were nearly all polychromatophilic in addition to having an irregularly-shaped and sometimes palely-staining nucleus.

CASE III.—Male, aged twenty-four years, seen first on August 27, 1899, with Dr. H. B. Favill. The patient first felt unwell in June of 1899. He was losing strength and his endurance lessened. He had charge of the finances of a rather large estate and had much responsibility. Without medical advice, he took a rest in the country during the latter part of June and the first half of July. He did not improve, and returned to Chicago. He noticed that he was very pale, breathless upon exertion, and that he was daily growing weaker. He had no pain and no disturbance of any kind excepting a sense of weakness and languor.

The physical findings were negative, excepting a rather rapid pulse, which was weak, and the temperature ranged from normal in the morning to 100° or 101° in the evening.

A blood examination made on August 27th showed hæmoglobin 37 per cent., with 488,000 reds per cubic millimetre, with a very high color index of 4.16, 6000 white cells, and 1704 nucleated red cells per cubic millimetre, of which 1224 were megaloblasts. There was marked poikilocytosis, and polychromatophilia was present.

On September 17th a third count was made, which gave 26 per cent. of hæmoglobin, 560,000 red cells per cubic millimetre, with the enormous number of 10,336 nucleated red cells per cubic millimetre, of which 7092 were megaloblasts There was marked irregularity of the nucleus, especially in the megaloblasts, with increased poikilocytosis and notable polychromatophilia.

During the last week of this patient's life his temperature rose to 104° in the afternoon of each day, with the pulse rapid and weak, and with symptoms of profound weakness, much dyspnœa, and dizziness. There was looseness of the bowels during the entire course, and in the stools were almost constantly found many infusoria, but no organism which could account for the anæmia. The patient died on September 22d. An autopsy was not obtained.

This case was remarkable as showing a very low red count, with an unusually high color index, which is explained by the very large number of macrocytes present. It is noteworthy that during the period in which he was observed the red corpuscles were practically stationary in number, while the hæmoglobin continued to fall. The leucocytes steadily increased with approaching death, and a few days before death there was an inundation of leucocytes, myelocytes, and nucleated red corpuscles, the degenerative megaloblasts predominating. The stained specimen gave findings similar to those of splenic myelogenous leukæmia; but the paucity of red corpuscles and hæmoglobin, the high color index, and the comparatively low white count, as well as the extreme poikilocytosis and polychromatophilia, would conclusively settle the diagnosis. The number of nucleated red corpuscles were enormous, with many of the nuclei undergoing fragmentation.

CASE IV.—Female, aged forty-three years; has borne three children. Was seen with Dr. McInnes, of Belvidere, Ill., September 5, 1899. The patient

has had chronic diarrhœa for three years, with loose, watery movements on rising, and occasionally one or more later in the day, uninfluenced by diet. For several months she has had progressive weakness and fatigue, associated with pallor. The skin has become yellow recently. There was slight swelling of the feet at night; nose-bleed slight on two or three occasions. There was palpitation of the heart. Patient had a desire for sour things; some eructation of gas, but has not vomited; was nervous. There was no blurring of vision. Weighed two years ago 135 pounds, now 107 pounds. Examination showed a systolic murmur at the apex transmitted into the axilla. No accentuation of the second pulmonic sound. A murmur, systolic in time, was heard in the aortic area. No venous hum in the neck. The spleen was palpable.

The patient was pale and the skin had a yellowish hue. The urine showed a slight trace of albumin, with a little pus. No tubercle bacilli in the urinary sediment. Feces, greenish and watery in color, showed no parasites. The blood showed hæmoglobin, 36 per cent.; red cells, 1,436,000; white cells, 4000, with poikilocytosis, and 72 nucleated cells per cubic millimetre, of which 54 were megaloblasts. There was irregularity of the nucleus of some cells, with poikilocytosis and polychromatophilia.

The patient improved upon restorative tonics of iron and arsenic, and the diarrhœa ceased with colonic flushings. During the winter of 1899 and 1900 the patient improved, and was considered well for two or three months. Her physician reported, in March, 1900, that she had again become very anæmic, with all the characteristics observed when first examined, and that she was then confined to bed. No further examination of the blood has been made.

CASE V.—Female, aged fifty-six years, admitted to the Cook County Hospital July, 1899. Seamstress, who gave a history of illness of about one year's duration. She was very pale; skin yellowish, and presented no physical findings of organic disease. There was a basic murmur, systolic in time, transmitted into the neck, but no venous hum. The urine was negative; the bowels were constipated. The patient complained of extreme weakness, shortness of breath on exertion, and dizziness when she changed her position suddenly.

Examination of the blood showed hæmoglobin, 25 per cent.; 848,000 red cells; 3500 whites; 21 nucleated red cells, of which 7 were megaloblasts. Poikilocytosis was very marked and polychromatophilia were present.

On restorative tonics the patient improved rapidly, so that on August 14th the hæmoglobin was 48 per cent., the red cells 1,624,000, still giving a high color index. There were 6000 whites and 12 nucleated red cells, all of which were normoblasts. The patient was so improved in strength that she left the hospital, and no further observation has been made.

In this case there was a rapid increase of the reds and of the hæmoglobin—100 per cent. in sixteen days. The color index was high and did not fall with the improvement, which is contrary to the usual rule in this disease. The leucocytes rose with improvement; the nucleated reds were few in

number; the megaloblasts disappeared with improvement, and poikilocytosis and polychromatophilia decreased.

CASE VI.—Male, aged sixty-one years, married, banker. Seen first on May 10, 1899. His family history was excellent. In the summer of 1898 he first noticed that he was easily exhausted on exertion. There was some coldness of the lower extremities, with numbness; he had dyspnœa on exertion and some dizziness. The appetite failed in March, 1899, and since then has been very poor; there was a bitter taste, which was present in many kinds of food. Has had some gas and weight in the stomach after eating. Bowels were usually regular; urination was normal; there was no pain. His present weight is 155 pounds; he has weighed 190 when well. He was very pale; there was a lemon-yellow color of the skin. There was a blowing systolic murmur over the præcordium—loudest in the mitral area; there was a venous hum in the neck; there were no other abnormal physical signs. There was a slight trace of albumin in the urine. The blood showed 828,000 red cells, with 25 per cent. of hæmoglobin, and 6000 whites. There were many nucleated red cells and marked poikilocytosis.

There was improvement under restorative tonic treatment, the patient presenting 50 per cent. of hæmoglobin and 2,080,000 red cells in September, after which there was a relapse. On October 30th the hæmoglobin was 40 per cent. and the red cells 1,912,000. There were 4 nucleated red cells per cubic millimetre, of which 2 were megaloblasts.

This patient has presented from the beginning all of the usual phenomena of a pernicious anæmia. When last heard from he was in California and becoming gradually worse. It is to be noted that there is a fall of the color index with improvement, with an inconstant leucocyte count, and but few nucleated red cells.

CASE VII.—Female, aged forty-seven years, was admitted to Cook County Hospital October 14, 1899. She had been transferred from the Detention Hospital for the Insane. She was of unsound mind; could not answer questions intelligently. Her friends gave a history of illness of about three months. Examination showed intense yellow pallor without emaciation. There were many small hemorrhagic spots in the skin of the body and the mucous membrane of the mouth. The retinæ were normal. There was a systolic apex murmur, with dulness on percussion, extending beyond the left nipple. Spleen not palpable; the bowels were constipated. Examination of the feces was negative. The temperature varied from 98° in the morning to 100.2° in the evening. The urine was negative. The blood gave 18 per cent. of hæmoglobin, 679,000 reds, 2000 white cells, marked poikilocytosis, with 315 nucleated red cells per cubic millimetre, of which 270 were megaloblasts.

On November 3d there was 10 per cent. hæmoglobin, 540,000 red cells, and 128 nucleated cells, of which 84 were megaloblasts. There was extreme irregularity of the nucleus, much poikilocytosis, and marked polychromatophilia. The patient died November 10th. An autopsy was not obtained.

Just before death the color index rose with the decline of the patient. The leucocytes increased slightly, the nucleated red cells diminished in number, while the poikilocytosis was extreme, and corresponded with the low red count.

CASE VIII.—Male, aged fifty-two years, shoedealer. Admitted to the Presbyterian Hospital in November, 1899. Ill for about a year. For seven months has been subject to fainting attacks, with much weakness, some shortness of breath and dizziness. There has been marked pallor for several months; bowels alternately loose and constipated; there has been some nosebleed. The patient has not lost in weight; the skin was lemon-yellow; pulse small, compressible, and weak. A blowing murmur was heard over the mitral area and at the base of the heart, transmitted into the neck. Spleen and liver negative; urine negative. Blood examination on December 11th showed 17 per cent. hæmoglobin, 760,000 red cells, 9000 whites, 135 nucleated reds per cubic millimetre, of which 81 were megaloblasts. On December 29th there was 20 per cent. of hæmoglobin, 880,000 reds, 2000 whites, and 15 nucleated reds, of which 9 were megaloblasts. There was much poikilocytosis and polychromatophilia. The patient died in January, 1900. Post-mortem revealed the usual findings of a pernicious anæmia, including fetal bone-marrow.

It is to be noted that in this case a few days before death the condition of the hæmoglobin and red corpuscles was stationary. The leucocytes fell with the decline, as did also the nucleated red cells. The poikilocytosis and polychromatophilia corresponded in degree with the number of red cells.

CASE IX.—Female, aged thirty-six years, housekeeper. Seen with Drs. Favill and Storer, September 27, 1899. Has suffered from goitre and symptoms of general nervousness for several years. For a year past has suffered from gradual increasing weakness, until prostration occurred, and has been confined to bed for the last three months. There has been a rapid heart, with tremor of the muscles, indigestion, with poor appetite and gradual emaciation. There has been headache, with many subjective nervous symptoms, including paræsthesia of the skin, numbness and coldness of the lower extremities, sleeplessness, and at times nausea and vomiting after some emotional disturbance.

Examination showed marked pallor of a yellow hue, emaciation, tremor of the extremities, especially upon exertion; a goitre of moderate size, vascular and throbbing; increase of the heart dulness beyond the left nipple; a murmur in the mitral area, systolic in character; a venous hum over the neck, and especially over the goitre; a pulse of 140 per minute, weak, quick, and compressible. Temperature subnormal in the morning and elevated to 99° and 100° in the evening. Negative findings over the abdomen; the urine free of abnormal elements; the pelvis normal. The blood on September 27, 1899, showed 20 per cent. of hæmoglobin, 864,000 red cells, 6000 whites, with 6 nucleated red cells per cubic millimetre—all megaloblasts. Some of the nucleated cells showed irregularity of the nucleus. There were poikilocytosis

and polychromatophilia. The clinical course and physical findings made a diagnosis of exophthalmic goitre probable, although there was no exophthalmos present upon examination, or a history of that sign. The patient died in November, 1899, showing no change in the condition enumerated above. No autopsy.

Neusser (*American Year-book of Medicine*, 1900, p. 127, quoted from the *Wiener klinische Wochenschrift*, April 13, 1899) describes a case of exophthalmic goitre occurring with pernicious anæmia. In the case reported here it is to be noted there was a small number of nucleated red cells, but they were all megaloblasts.

CASE X. (See Chart I.)—Male, aged thirty-six years, a collector, married. Patient had a severe attack of influenza in January, 1899. He was confined to bed for ten days, otherwise his health has been good since childhood. Following illness in January he had remained unwell, had grown pale, and had noticed a progressively increasing weakness, with slight dizziness and dyspnœa upon exertion. The extremities were often cold, and there was palpitation of the heart at times. The appetite was good and digestion unimpaired. The bowels were slightly constipated. The patient had no other discomfort than those enumerated.

Examination: No emaciation, lemon-yellow pallor, a few petechial spots about the chest and base of the neck in front, and a few in the roof of the mouth. There was a murmur over the base of the heart transmitted into the neck, and a venous hum was also heard over the large vessels of the neck. The urine was normal and the physical findings over the abdomen negative. The blood showed no plasmodia, 33 per cent. of hæmoglobin, 2,000,000 red cells, 16 nucleated cells, of which 8 were megaloblasts; poikilocytosis and polychromatophilia present.

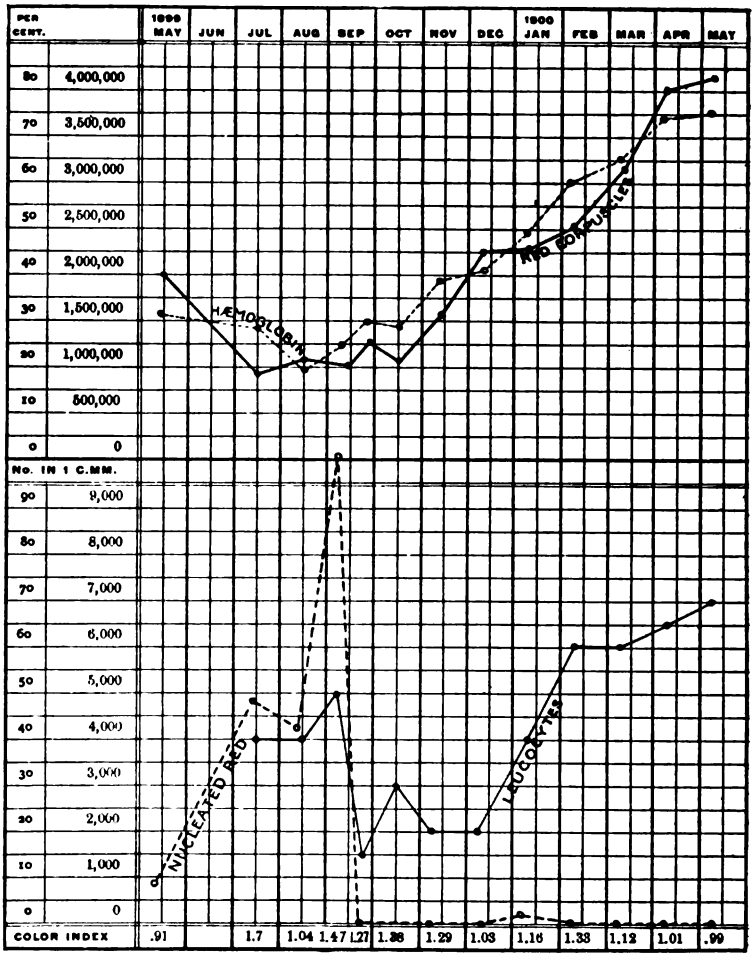
Upon restorative tonics the patient did not improve. There was a gradual decline in health, evidenced by the blood findings, which, on September 6th, showed hæmoglobin 27 per cent., 1,800,000 reds, 5000 whites, 100 nucleated red cells, of which 80 were megaloblasts, with the ordinary associated irregularity in size and shape of cells, and polychromatophilia. Improvement occurred from this time onward, until at the last examination there was 74 per cent. of hæmoglobin, 4,010,000 red cells, 6500 white cells, and no nucleated cells.

This patient is still under observation and presents phenomena which unmistakably confirm the first diagnosis and show that he is still ill, although the blood condition is so much improved.

In this case the color index was nearly always high, the tendency being a slight decrease with the improvement. The leucocytes increased usually with the general improvement of the patient. There was a flood of nucleated red cells, the so-called crisis before improvement, and these disappeared

with the improvement. Megaloblasts predominated; poikilocytosis and polychromatophilia were markedly less than usual, with a corresponding red count in other patients. The improvement wave in this case continued steadily for about seven months.

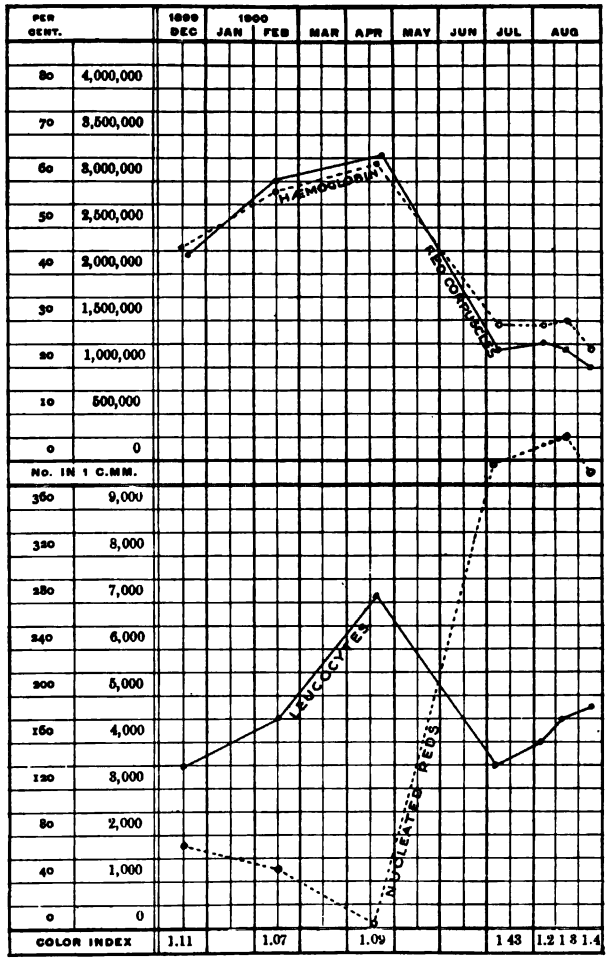
CHART I.



CASE XI. (See Chart II.)—Male, aged forty-five years, lawyer; gives a history of illness extending over one year. Seen in consultation with his physician, Dr. A. J. Coey. Patient has always been a hard worker, taking but little rest, and having large responsibilities. He has suffered from no

illness during his life until at present. An examination on December 29, 1898, showed no loss of weight, but a lemon-yellow pallor, with a small, quick, compressible pulse, and normal temperature; a weak heart-beat, with a faint systolic murmur at the base; no venous hum in the neck. Negative

CHART II.



findings over the chest, excepting as stated, and over the abdomen. Urine normal. Patient complained of weakness, with shortness of breath on exertion, dizziness, palpitation of the heart, poor appetite, and some gaseous indigestion. Blood count showed 40 per cent. of hæmoglobin, 2,228,000

red cells, 3500 whites, 70 nucleated reds—all of them normoblasts. Poikilocytosis and polychromatophilia present.

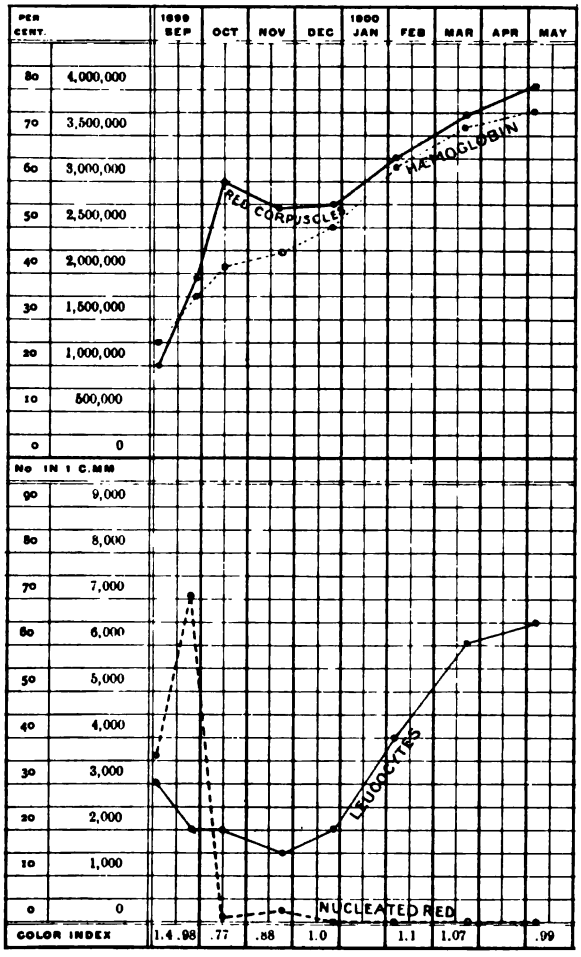
During the remainder of the winter the patient improved to some extent; his red cells increased to 3,276,000, his hæmoglobin to 65 per cent., white cells to 7200, and nucleated cells disappeared. There was a relapse in June, 1899, and on July 31st the hæmoglobin was 23 per cent., the red cells 886,000, the whites 3500, and 392 nucleated cells were found per cubic millimetre, of which 308 were megaloblasts. Irregularity of the nucleus; poikilocytosis and polychromatophilia were marked. The physical findings were practically the same as when the patient was first seen six months before. He declined from this time on, and died the latter half of August. About two weeks preceding his death the patient had direct transfusion of six ounces of human blood by his own request. This was followed by no improvement in the blood, nor did hæmoglobin appear in the urine. Autopsy revealed the ordinary findings of a pernicious anæmia, including the fetal bone-marrow.

The color index diminished with improvement, but did not change to the degree often seen in other cases. This was probably due to the fact that the improvement was very slow, so that the hæmoglobin kept pace with the improvement in the number of red cells. The leucocyte increase occurred with improvement, as is the rule; but there was only a slight leucocyte increase before death. The nucleated red cells were large in number, but did not increase to any great extent immediately preceding death, as was noted in Case III. The poikilocytosis and polychromatophilia corresponded in degree to the red count. The improvement wave lasted about five months.

Case XII.—Female, aged sixty years; has borne nine children. Seen first as a private patient on October 24, 1899. Family history good. Has had dyspepsia with the formation of a good deal of gas at times for the last two years. For two years her health has been failing; for six months had a dull, gnawing pain in the region of the stomach—not influenced by food. Has vomited two or three times a week for the last two or three months, and nearly every day for the last two weeks. No blood in the vomited matter; appetite usually good; bowels were constipated. Complained chiefly of weakness and want of endurance, palpitation of the heart, shortness of breath, with dizziness and faintness. There was some frontal headache and paræsthesia, especially of the lower extremities; there has been some loss in weight—from 165 to 130 pounds; there has been a gradually increasing pallor. Examination showed a yellow pallor with pale mucous membranes; pulse rapid, weak, and compressible; capillary pulse in the lips. Heart-sounds were weak, without murmurs. Abdomen and pelvis negative. The urine showed a slight trace of albumin; otherwise normal. The blood showed 32 per cent. of hæmoglobin, 2,100,000 reds, 8000 whites, and 40 nucleated red cells per cubic millimetre, of which 24 were megaloblasts. Irregularity of the nucleus; poikilocytosis and polychromatophilia present. Under restorative tonics the patient improved in strength, and on December 6th the

hæmoglobin was 48 per cent., reds 2,348,000, whites 9000, nucleated red cells 8, of which 4 were megaloblasts. The patient lives in Iowa, and a relative has just informed me that she continued to improve until the first part of March, but since that time there has been a return of the old symptoms, with increasing pallor, weakness, etc.

CHART III.



The color index rose with improvement, which was gradual, and the rise was, therefore, slight. The leucocytes were inconstant in number; the nucleated red cells decreased with the improvement, and the megaloblasts lost

their preponderance over the other forms with improvement. The poikilocytosis and polychromatophilia corresponded with the red count.

CASE XIII. (See Chart III.)—Female, aged sixty years, copyist; has borne two children. Was admitted to the Cook County Hospital on September 8, 1899. For six months the patient has complained of weakness, faintness, shortness of breath, palpitation of the heart, coldness of the extremities, and general nervousness. She has had nose-bleed twice. There has been no loss in weight, but the symptoms above enumerated have become so marked that she was obliged to go to bed. Examination showed a lemon-yellow pallor, with some œdema of the eyelids and of the ankles. Pulse was small, rapid, compressible, and weak. A soft murmur was heard over the heart, transmitted into the vessels of the neck. A venous hum was also heard in the neck. The spleen was palpable and the liver extended two finger-breadths below the right costal arch. The urine was normal and the pelvis negative; there were no hemorrhages of the skin and the retinæ were normal. The temperature was elevated the last two days, following an attack of diarrhœa; the stool was watery and loose and contained no parasites. A blood examination showed 25 per cent. of hæmoglobin, 960,000 reds, 3000 whites, 36 nucleated cells per cubic millimetre, of which 12 were megaloblasts, 12 microblasts, and 12 normoblasts. Irregularity of the nucleus, poikilocytosis, and polychromatophilia present.

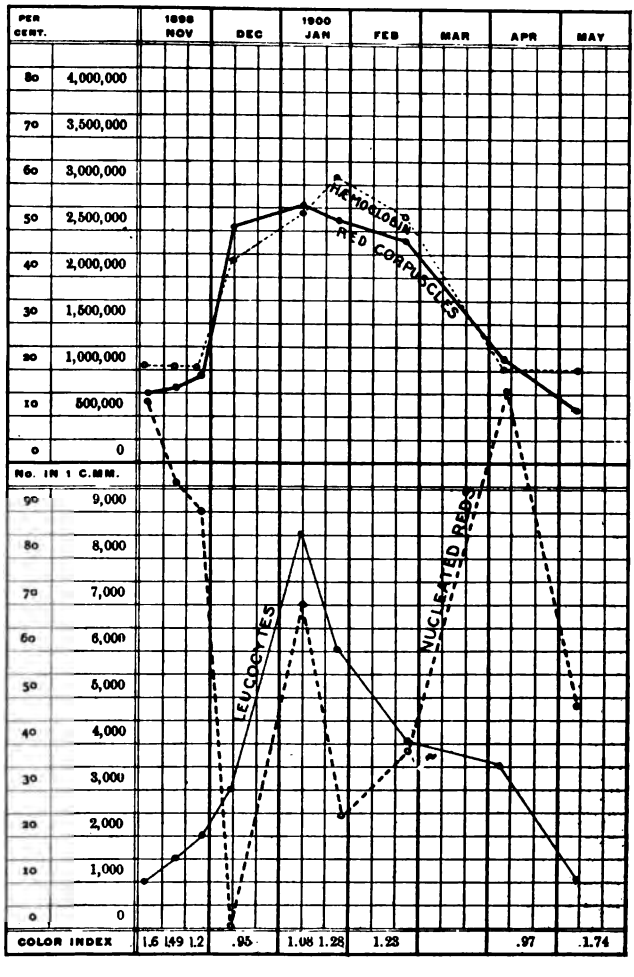
Under restorative tonic treatment the patient improved rapidly, and on November 25th, just previous to leaving the hospital, the hæmoglobin was 44 per cent., red cells 2,736,000, white cells 1500, with 3 nucleated cells—all megaloblasts, present with a continued but lessened poikilocytosis and polychromatophilia. The improvement continued. A blood examination made on March 21st gave hæmoglobin 72 per cent., red cells 3,720,000, the whites 6000, no nucleated cells, but poikilocytosis and polychromatophilia still present. In spite of the evident improvement in the blood the patient complained of great weakness. She is undoubtedly at the top of an improvement wave.

CASE XIV. (See Chart IV.)—Female, aged twenty-nine years, married; has borne no children. Was admitted to the Cook County Hospital on November 3, 1899. The patient gives a negative history as to previous illness of any severity. Present illness began six months ago, with diarrhœa in August and September. She has also had some cough with bloody expectoration. There has been shortness of breath, with palpitation, great weakness, dizziness of changing the position of the body suddenly, dimness of vision, some headache and intercostal pains, and paræsthesia of hands and feet. Examination showed a lemon-yellow color without emaciation. The pulse was rapid and feeble; a blowing murmur was heard over the base of the heart, transmitted into the neck; there was no venous hum. The lungs, the abdomen, and the urine were negative; the stools were formed, and no parasites were found. The blood examination showed hæmoglobin 22 per cent., red cells 744,000, white cells 1000, 115 nucleated cells per cubic milli-

metre, of which 85 were megaloblasts. Poikilocytosis was very marked and polychromatophilia was present.

Under restorative tonic treatment the patient improved gradually, as is shown by numerous blood examinations, until January 16, 1900, when the

CHART IV.



best condition prevailed. At this time the hæmoglobin was 62 per cent., reds 2,650,000, whites, 6000, nucleated red cells 24, of which 12 were megaloblasts; poikilocytosis much less than formerly, and only slight polychroma-

tophilia. At this time the patient complained of soreness of throat, and an examination showed a syphilitic gumma of the soft palate. She was placed upon large doses of iodide of potash and inunctions of mercury. The gumma rapidly disappeared, and the throat was healed within one month. From this date, however, the patient again declined in health, lost in weight and strength, had dizziness, dyspnœa, and palpitation on exertion. There was a murmur at the apex and the base of the heart, and a very weak and compressible pulse. An examination made on April 10th showed hæmoglobin 20 per cent., a fall of over 40 per cent. in less than three months; red cells 1,132,000, whites 3500, nucleated cells 116 per cubic millimetre, of which 102 were megaloblasts; increased poikilocytosis and polychromatophilia.

This patient suffered from syphilis, although she denied all knowledge of acquiring the disease. What relation the syphilis bore to the blood state is questionable. Under antisyphilitic treatment the blood became rapidly worse; but this is, of course, no proof that the blood state even of pernicious anæmia may not be caused by syphilis.

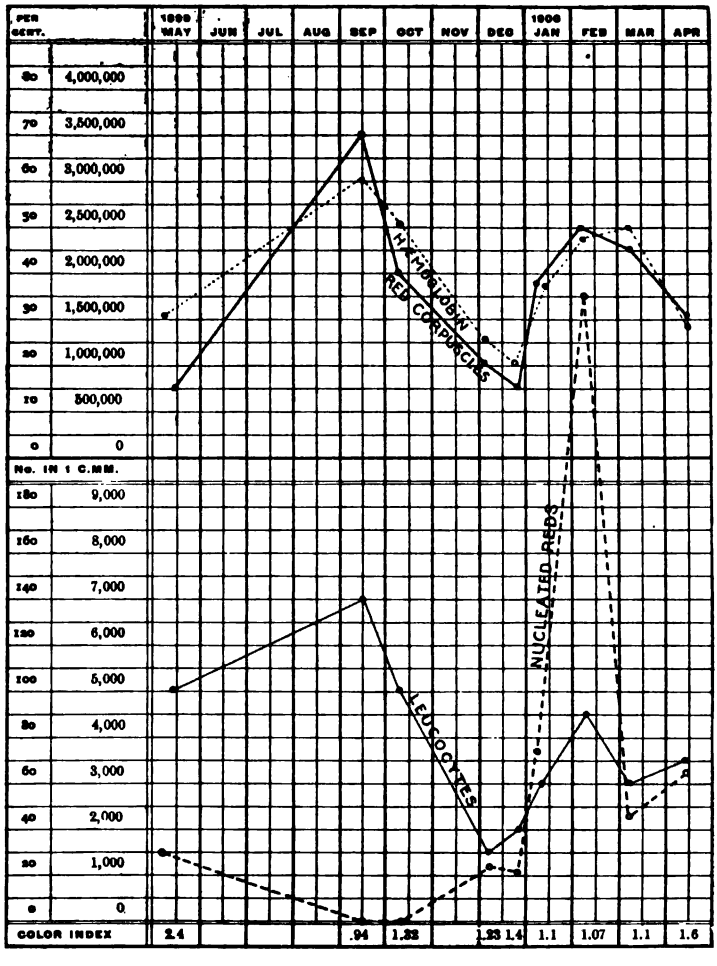
Following the rule, the color index fell with improvement in this case, but continued to fall with the decline. The leucocyte count corresponded in degree to the number of reds and the percentage of hæmoglobin. In this case, too, there was a flood of nucleated reds before improvement, corresponding partially to von Norden's law. The nucleated reds disappeared once during the stage of improvement, and increased again with the decline. The megaloblasts were also in excess; the poikilocytosis and polychromatophilia corresponded to the number of reds. The improvement wave continued for about five months.

CASE XV. (See Charts V. and VI.).—Male, aged forty-three years, married, an engineer, was admitted to the Cook County Hospital on April 19, 1899. Gave a negative history of tuberculosis and carcinoma in the family, and denied venereal disease. Was always healthy until present trouble. For two years has felt tired and weak, sleepy, and has been told that he looked paler than usual. Was annoyed by a pain and weight in the stomach, with eructations of gas after meals. Twenty-one months ago gave up work and was in a hospital for three weeks. He again went to work after three weeks for about a year. During the last period, when at work, he was troubled with shortness of breath and palpitation upon severe exertion, and frequently had bleeding of the gums. Recently he has had no appetite, has had pain in the stomach after eating, and has vomited at times soon after the meal. The bowels have been constipated.

Examination showed a lemon-yellow pallor without much loss of weight, with general negative findings, including the chest, the abdomen, and the kidneys. After a test meal no hydrochloric acid was found in the stomach contents, while lactic acid was in excess. A blood examination made on May 20, 1899, showed 32 per cent. of hæmoglobin, 726,000 reds, 5000 whites, 30 nucleated cells per cubic millimetre, of which 20 were megaloblasts, poikilocytosis, and polychromatophilia.

The patient improved until October, 1899, the red cells increasing to 3,500,000 and hæmoglobin to 60 per cent., the nucleated cells disappearing. Then there was a relapse, with a low ebb in December, when the hæmoglobin fell to 22 per cent., the red cells to 880,000, the nucleated reds to 32

CHART V.

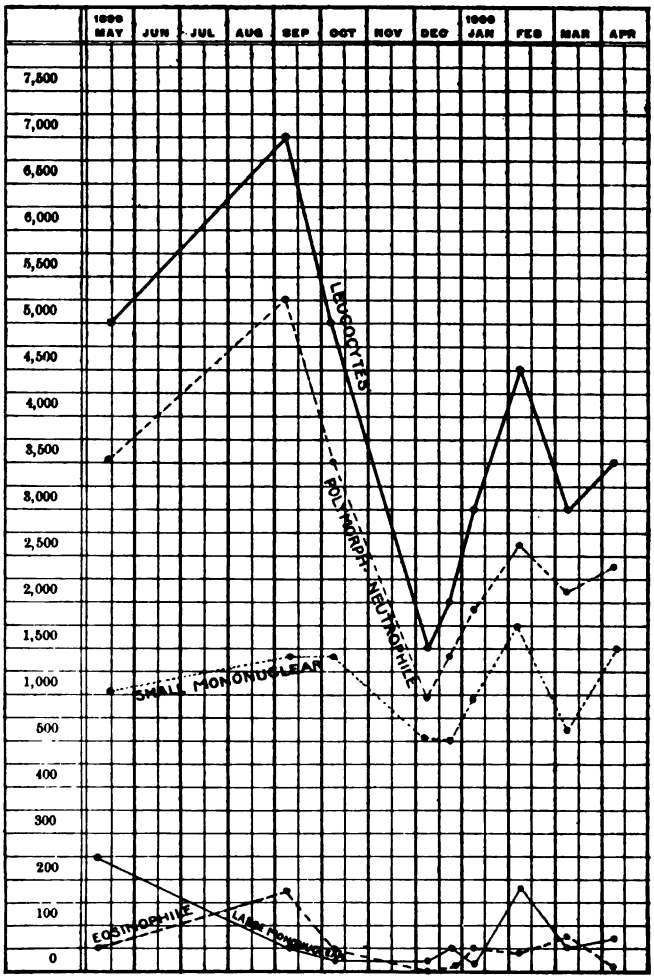


per cubic millimetre, of which 28 were megaloblasts, while poikilocytosis and polychromatophilia were very marked. Again, improvement occurred under restorative tonics and rest in bed until the latter part of March, 1900, since which time there has been again a decrease in the hæmoglobin, in the red

cells, and an increase in the nucleated reds, and in the regularity of the cells, and increased polychromatophilia.

This man presented in every way a classic case of pernicious anæmia. His physical findings were negative. Frequent examinations of his stomach con-

CHART VI.



Differentiation of leucocytes in absolute numbers per cubic millimetre.

tents after a test meal showed the constant absence of hydrochloric acid, free and combined, and lactic acid always present, usually in large amount.

The color index was nearly always high, but fell with improvement and increased with each decline. The nucleated cells disappeared in the first improvement wave and reappeared with the decline. They increased with the second improvement, amounting to a crisis. The first improvement wave lasted six months, the second about four months. Poikilocytosis was very marked, even when the reds were in largest number. Polychromatophilia varied with the number of reds. The patient died at his home in South Chicago, May 21, 1900. No autopsy was made because the death was not reported to the writer until too late.

CASE XVI.—Male, aged forty-eight years, married, a capitalist. Seen January 1, 1900, with Dr. Franklin Hays, of Indianapolis, Ind. Gives an excellent family history, with good habits. Venereal disease denied. Has not been well since 1895, when he was almost suffocated by smoke while exhibiting an invention to protect firemen from smoke. Since then has had suffocative attacks, with dizziness and occasionally abdominal pain. Bowels have been constipated; he has lost in strength without loss of weight. There have been palpitation, shortness of breath on exertion, and dizziness when moving suddenly or under excitement. Appetite has been variable and digestion usually good. Was in Europe in the fall of 1899, and a blood examination was made in London by Dr. Severs, which showed hæmoglobin 25 per cent., reds 2,200,000, and whites 20,500. For the last six months there has been a more rapid decline in strength and endurance until at present the patient is confined to bed by extreme weakness.

Examination showed a very pale-lemon tint, without loss of weight. The pulse was small, quick—108 per minute; the temperature 102° at the time of examination. A loud systolic murmur was heard over the præcordium—loudest in the mitral area. The second sound accentuated in the pulmonic area. No murmur in the vessels of the neck. A few moist râles were heard on deep inspiration over the lower portion of the lungs behind. The abdomen showed the liver with normal area, the spleen palpable; rectum negative. A small nodule, the size of a navy bean, in the left epididymis. Eye-grounds normal. The blood showed hæmoglobin 15 per cent., red cells 912,000, nucleated cells 21 per cubic millimetre, of which 14 were megaloblasts. Marked irregularity of nucleus; poikilocytosis present, with polychromatophilia.

A blood examination made June 6, 1900, showed hæmoglobin 19 per cent., red cells 762,000, whites 7000, nucleated reds, 21 per cubic millimetre, of which 14 were megaloblasts and 7 normoblasts. Polychromatophilia and poikilocytosis present.

This patient presented every condition, as far as the appearance and physical findings go, of a pernicious anæmia; and although the color index is relatively low, the other conditions of the blood make the diagnosis practically certain.

CASE XVII.—Male, aged forty-six years, married, American; was seen on March 28, 1900. Negative history as to inherited disease; good habits.

Venereal disease denied. Lived in South Dakota several years, and immediately preceding the present illness used the alkaline waters of that region as a drink. Present illness began about fifteen months ago. He first noticed signs of weakness and lessened endurance, then had a rather severe serious diarrhœa. He noticed that the skin was yellowish and very pale. Since that time has had some fermentative dyspepsia, with diarrhœa off and on, the bowels usually loose.

During the first half of 1899 there was some improvement, when the patient came to Wisconsin to remain with his father's family. He gradually became weaker, and was confined to bed in September, 1899, and had a severe watery diarrhœa. He lost some in weight. Again there was improvement until February 1, 1900. Since that time there has been a rapid decline of health, with weakness, palpitation of the heart, dyspnœa on exertion, and a suffocative feeling, with post-sternal pressure, sometimes radiating to the arms when excited or when walking up stairs. In February, 1900, a blood examination made by the Columbus Medical Laboratory of Chicago showed hæmoglobin 37 per cent., reds 1,702,000.

Examination showed a well-nourished man as to weight, with a lemon-yellow pallor. Pulse small, 130 per minute; heart area normal; a soft systolic murmur at the base and apex, the murmur transmitted into the neck. A loud venous hum in the neck. The lungs, the abdomen, and the pelvis negative; slight œdema of the ankles. The retinæ normal; no petechial spots; the urine contained a great number of crystals of uric acid, but no abnormal ingredients. Blood examination showed hæmoglobin 20 per cent., reds 701,200, whites 4140; 32 nucleated cells per cubic millimetre, of which 24 were megaloblasts. Poikilocytosis was very marked and polychromatophilia present. This case is one of undoubted pernicious anæmia.

The case shows a very low red count, and is remarkable in that the megaloblasts are very large and show a very intense irregularity in shape of the nucleus, characteristic of extreme degeneration. Poikilocytosis was extreme.

The patient died at his home in Wisconsin the first half of April. No autopsy.

Case XVIII.—Male, aged fifty-five years, married, American, civil engineer. Seen April 1, 1900, with Drs. Staples and Hancock, of Dubuque, Iowa. Family history negative; venereal history negative; good habits. His wife has borne no children. During the summer of 1899 the patient noticed that his color was not as ruddy as formerly, and that he had lost energy and became fatigued quickly. Dr. Hancock found negative physical conditions except of the blood, which, on November 12th, gave 2,550,000 red cells. The hæmoglobin was not estimated.

Restorative tonics in the form of iron and arsenic were used, but the patient gradually lost ground. On January 2d, Dr. Hancock found red cells 1,980,000, with many megaloblasts and marked poikilocytosis. Patient's weight was 155 pounds, the usual weight for the last few years. He complains of great weakness and prostration. He had palpitation of the heart,

ringing in the ears, and was dizzy when he changed the position of the body. Appetite was good until recently; the bowels were usually constipated. The patient had no pain; there was a lemon-yellow color skin. Pulse was small, weak, and 80 to the minute. There was a soft systolic murmur heard at both the apex and base of the heart—loudest over the aortic area—transmitted into the neck. The second sound in both the aortic and pulmonic areas was accentuated. There was a venous hum in the neck. The lungs were negative; the spleen was negative; the liver extended from the sixth rib to one inch below the costal margin in the mammary line, and the edge was hard and resistant. The pelvis was negative; the reflexes, both deep and superficial, were normal; the eye-grounds were normal; the urine was normal, with much uric acid deposited in crystals. Blood showed hæmoglobin 20 per cent., 1,674,000 reds, 1140 whites, with 5 nucleated red cells, of which 4 were megaloblasts. Poikilocytosis was very marked, and polychromatophilia was present.

On April 18th a blood count was made by Dr. Hancock, which showed hæmoglobin 20 per cent., reds 1,342,000, whites 1750, with many megaloblasts, and marked poikilocytosis. This case is an undoubted one of pernicious anæmia without discoverable cause.

The color index was below normal, but the nucleated red cells were very large and showed degenerative nuclei. A small white count is notable.

CASE XIX.—Male, aged fifty-two years, banker. Seen on April 13, 1900, with his physician, Dr. B. F. Landis. Family history excellent. Has never used alcohol or tobacco, and denies venereal disease. Has always led a sedentary life. No previous illness except the diseases incident to childhood. Two years ago first noticed lessened energy and strength, gradual decline without incident until the fall of 1899; then was very pale, weak, and without much energy or endurance. Remained up and about until the middle of March, 1900, but since then has been confined to bed.

Examination showed a lemon-color pallor without loss of weight. Pulse weak, 90 to the minute. Heart-sounds weak; a systolic murmur, heard loudest in the mitral area, and also at the base, transmitted into the vessels of the neck; a venous hum over the veins of the neck. Negative general findings as to liver, spleen, pelvic organs, and the eye-grounds were normal. Cutaneous sensations normal. The breath was fetid and the tongue was covered with a white fur. Urine was normal. Blood showed 25 per cent. of hæmoglobin, reds 156,000, whites 5336, 26 nucleated red cells, of which 24 were megaloblasts. Poikilocytosis very marked and polychromatophilia present.

On June 9, 1800, a blood examination gave hæmoglobin 30 per cent., red cells 996,000, whites 3330, 10 nucleated red cells (all megaloblasts) per cubic millimetre.

The patient died June 16th. No autopsy was allowed.

CASE XX.—Male, aged twenty-six years, single, American; was admitted to the Presbyterian Hospital, Chicago, June 1, 1900. No tuberculosis or

history of carcinoma in the family; denies venereal disease. Had the usual diseases of childhood before the fifteenth year. In 1890 had a severe attack of grippe; not as strong as before that time. Present illness commenced after an attack of grippe in December, 1899. A year ago noticed weakness, lessened endurance, palpitation of the heart, and dyspnœa on exertion. Tingling formication, numbness and coldness of feet and legs occurred in January, 1899, and have persisted. Was told he was very pale; did not lose in weight; appetite and digestion remained good and the bowels were usually regular. Had some fever, he thinks, during the afternoon on several occasions. Contracted a cold two weeks ago, and since that time has had a slight cough, with some yellowish sputa.

On examination bodily weight was well preserved; skin very pale and lemon-yellow tint; mucous membrane very pale. Negative physical findings as to lungs, liver, and gastro-intestinal tract. Urine negative; spleen palpable. A blowing systolic murmur was heard in the mitral and aortic areas—not transmitted. A venous hum was heard over the large vessels of the neck. Pulse 100 per minute, quick, and somewhat water-hammer in character; a capillary pulse in mucous membrane of the lips. The knee-jerks absent; cremasteric reflexes present. Skin of the lower extremities respond to test for tactile temperature and pain sensations. Subjective paræsthesias of legs present. The blood showed red cells 756,000, white cells 3008, hæmoglobin 30 per cent. No differentiation of white or red cells was made. June 15th a second blood examination gave reds 980,000, whites 8000, and hæmoglobin 26 per cent. Poikilocytosis was very marked. There were 660 nucleated red cells per cubic millimetre, of which 400 were megaloblasts.

GENERAL CONCLUSIONS.

Of the twenty cases twelve were males and eight females. The average age was forty-four years—the youngest twenty-four, the oldest sixty-two. No exciting cause could be found in any case. There was no special relation to the use of alcohol, nervous shock, overwork, or to previous disease, excepting possibly in the one case where syphilitic gumma of the soft palate occurred.

The symptoms were: weakness, which was a constant symptom, never disappearing, and present in some degree even when the patient was at the top of the wave of improvement; and dyspnœa and palpitation occurred at some time or other during the course of the disease in every patient. Gastro-intestinal disturbance of some kind, usually fermentative dyspepsia with constipation or diarrhœa, was the rule. A few cases showed a constant tendency to diarrhœa.

The nervous symptoms were frequent, especially paræsthesias of the lower extremities, and headache with dizziness was common.

Sleeplessness and restlessness occurred in the late stages of the fatal cases.

The lemon-yellow tint was present in every case. In the great majority of the cases there was preservation of the body weight.

Cardio-vascular disturbance was an invariable feature. In every case there was either a murmur over the heart or in the neck, and the radial pulse was weak and compressible.

There was splenic enlargement in five cases. The liver was palpable and enlarged in three cases. In only three cases were the stomach contents examined after a test meal. Free hydrochloric acid was absent in all cases.

The temperature was elevated, as a rule, but was slight and never high, excepting a few days before death in some of the fatal cases.

A slight albuminuria occurred in five cases.

The stools were negative as to parasites in all but one. In this one infusoria in large numbers were constantly present and associated with diarrhœa.

Hemorrhages in the skin, either petechiæ or ecchymoses, occurred in the majority of cases. Retinal hemorrhages, demonstrated by the ophthalmoscope, occurred in four cases.

The hæmoglobin varied from 15 to 74 per cent. (Fleischl) and the red corpuscles from 156,000 to 4,000,000. The color index in 53 of 66 observations was above normal. The lowest was 0.66, the highest 8.9 (?). Four cases showed the color index either constantly or usually low. In eight cases the low-color index occurred at some time during the disease. The fall in the color index during rapid improvement took place in five of six cases, the corpuscular richness often becoming less than normal. The hæmoglobin in the course of time caught up with the reds (see charts). When improvement was gradual the increase in both elements was *pari passu*. The specific gravity bore a more constant relation to the number of red corpuscles than the hæmoglobin. During rapid improvement it was noticed that there was a tendency of the hæmoglobin to lag behind the other solids of the blood in their upward course (see charts).

The leucocytes on the average were below normal. They generally corresponded to the degree of anæmia, increasing during improvement and decreasing during decline. They increased in two cases just before death, a terminal leucocytosis.

A differential count (see Chart VI.) of stained specimens showed an average of 29½ per cent. of mononuclear cells, which is about normal. Very frequently there was a percentage increase of the small mononuclear cells. This would, at first glance, look like an absolute increase of the small mononuclears, and possibly account for the incorrect statements made by authors upon this point. The increase is only relative. It has been observed in these cases that the high percentage count of the leucocytes was nearly always accompanied by a small number of leucocytes per cubic millimetre, thus bringing the absolute number of lymphocytes per cubic millimetre within the normal limits. What actually took place was a diminution in the number of polymorphonuclear neutrophiles, both relative and absolute.

The eosinophiles showed a disposition to increase with improvement and to diminish with the failing health, but this behavior was too fickle to enable one to formulate a rule concerning them.

The myelocytes were most abundant, broadly speaking, when the patient was low, but they appeared to be of little diagnostic or prognostic importance. These cases seemed to show that the nucleated red cells are an essential feature of the disease. They were present in every case, although they often disappeared when the patient made a decided gain in health. The actual number was sometimes very large, in one case 10,336 per cubic millimetre, but more often it was small. The average number present in a cubic millimetre, with the exception of the case in which the number was so large, was 71. With this small number it often requires a prolonged search to discover them in the ordinary smear.

In individual cases a comparison of the number of nucleated red cells present from time to time was of considerable value, but when a small number was present it was not necessarily a favorable sign. Many subjects were characterized throughout by a scarcity of nucleated reds, and again they were diminished before death. The *quality* of the nucleated cells seems of greater significance than the number. The regenerative forms, or normoblasts, are of little consequence, but the degenerative forms, or megaloblasts, are very characteristic. In many cases they were present, and, in fact, the diagnosis could not well be made in their absence. The proportion of megaloblasts varied with the severity and stage of the disease, usually gaining a numerical ascendancy over the normoblasts when the disease was advanced.

Irregularity of the nucleus in the normoblasts often means an attempt at division; in the megaloblast it is more often an incident in the process of degeneration and absorption of the nucleus. Megaloblasts, therefore, which have irregular nuclei represent a greater degree of degenerative change than the ordinary variety. This peculiarity was noted in almost every one of the series, and often when other findings were not decisive. This variety of nucleus is probably seen rarely, if at all, in secondary anæmias.

Poikilocytosis was present in all cases, and in no case did it entirely disappear at any stage of the disease, including the period of greatest improvement.

Polychromatophilia was present at some time in all of the cases, but was not a constant factor during the course of the cases, and especially during the stage of improvement.

To my assistant, Dr. Joseph A. Capps, I desire to acknowledge much valuable aid in the collection of clinical data and in making blood examinations.

Case No.	Date.	Haem. per ct.	Specific gravity.	Reds.	Color index.	Whites.	Small mononuclear.	Large mononuclear.	Polymorphonuclear neutrophile.	Eosinophile.	Myelocytes.	Nucleated reds in c.mm. Normoblasts.	Microblasts.	Megaloblasts.	Total.	Irregularity of nucleus.	Poikilocytosis.	Polycromatism.	Remarks.
	1899																		
I.	Mar. 18	24	.....	1,400,000	0.94	21,000	6.2	2.8	90.7	0.3	0.0	84	0	84	168	+	++	+	Died Mar. 20, 1899.
II.	Aug. 31	34	.....	1,010,000	1.85	6,000	38.0	1.4	60.0	0.4	0.2	39	0	189	228	++	++	+	Died Sept., 1899.
III.	Aug. 27	37	1089	488,000	4.16	6,000	32.4	8.4	52.0	0.4	6.8	144	360	1224	1704	+	++	+	
	Sept. 6	34	1036	530,000	3.52	9,000	38.4	5.6	44.8	0.8	10.4	1458	1332	2700	5420	+	++	++	
	Sept. 17	26	1031	560,000	2.55	34,000	25.9	10.1	34.2	0.4	29.4	1768	1496	7092	10336	++	++	+++	Died Sept. 22, 1899.
IV.	Sept. 5	34	1039	1,436,000	1.30	4,500	28.8	0.8	68.0	1.6	0.8	18	0	54	72	+	+	+	
V.	July 29	25	.....	848,000	1.62	3,500	27.0	2.0	68.0	3.0	0.0	7	7	7	21	+	++	+	
	Aug. 14	48	1046	1,624,000	1.03	6,000	21.0	3.0	71.6	4.0	0.4	12	0	0	12	0	+	sl	Great improvem't.
VI.	May 10	21	.....	828,000	1.39	6,000	.....	.....	.....	.....	.....	+	...	+	...	...	++	+	
	Sept. 27	55	.....	2,080,000	1.26	7,600	.....	.....	.....	.....	+	+	...	+	...	...	+	+	Improvement.
	Oct. 30	40	.....	1 912,000	1.15	2,000	27.0	2.0	71.0	1.0	0.0	2	0	2	4	+	+	+	
VII.	Oct. 20	18	1032	679,000	1.45	2,000	28.0	1.0	69.0	1.0	1.0	45	0	270	315	++	+++	++	
	Nov. 3	20	1033	540,000	2.03	3,000	33.2	2.4	62.4	0.8	1.2	30	14	84	128	++	+++	++	Died Nov., 1899.
VIII.	Dec. 11	17	1028	760,000	1.23	9,000	27.0	0.6	71.2	1.2	0.0	54	0	81	135	+	++	++	
	Dec. 29	20	1028	880,000	1.25	2,000	13.6	2.0	83.2	0.8	0.4	6	0	9	15	+	++	++	Died Jan., 1900.
IX.	Sept. 27	21	1029	864,000	1.22	6,000	38.0	1.4	60.0	0.4	0.2	0	0	6	6	+	+	+	Died Nov., 1899.
X.	May 9	33	.....	2,000,000	0.91	.....	.....	.....	.....	.....	.....	8	0	8	16	...	+		
	July 25	28	1029	900,000	1.7	4,000	48.0	3.0	48.0	1.0	0	44	0	4	48	+	+	+	
	Aug. 9	21	1029	1,110,000	1.04	4,000	52.0	1.2	46.8	0.0	0	24	0	16	40	+	+	+	
	Sept. 6	27	1031	1,008,000	1.47	5,000	60.8	1.2	37.2	0.8	0	20	0	80	100	+	+	+	
	Sept. 30	30	1033	1,300,000	1.27	1,500	49.2	2.4	48.0	0.0	0	0	0	0	0	0	+	+	
	Oct. 14	28	1032	1,118,000	1.38	3,000	43.5	0.5	55.0	0.5	0.5	0	0	0	0	0	+	+	
	Nov. 5	38	1038	1,620,000	1.29	2,000	46.5	1.0	52.0	0.0	0.5	10	0	0	10	0	+	sl	Improvement.
	Dec. 5	42	1042	2,240,000	1.03	2,000	42.0	2.0	55.0	1.0	0	0	0	0	0	0	+	sl	"
	1900																		
	Jan. 7	49	1047	2.312,000	1.16	4,000	45.0	2.0	51.0	2.0	0	1	0	3	4	sl	+	sl	"
	Feb. 5	62	1051	2,550,000	1.33	6,000	40.0	1.0	58.0	1.0	0	0	0	0	0	0	sl	sl	"
	Mar. 3	65	1053	3,200,000	1.12	6,000	34.4	4.8	60.8	0.8	0	0	0	0	0	0	sl	sl	"
	April 6	74	1058	4,010,000	1.01	6,500	36.5	6.0	56.5	1.0	0	0	0	0	0	0	sl	sl	"
	May 5	75	1060	4,146,000	0.99	7,000	40.0	2.0	57.0	1.0	0	0	0	0	0	0	sl	sl	"
	June 2	80	1060	4,210,000	1.04	6,200	37.0	6.0	56.0	1.0	0	0	0	0	0	0	sl	0	"
	1898																		
XI.	Dec. 29	45	.....	2,228,000	1.11	3,500	28.0	5.0	69.0	2.0	1	70	0	0	70	...	+	+	
	1899																		
	Feb. 14	58	.....	2,988,000	1.07	4,600	22.0	6.0	67.0	5.0	0	55	0	0	55	...	+	+	Improvement.
	April 28	65	.....	3,276,000	1.09	7,200	23.0	8.0	66.0	3.0	0	0	0	0	0	0	+	0	"
	July 31	23	1083	886,000	1.43	3,500	30.4	4.0	63.1	2.0	0.5	70	14	308	392	++	++	++	Decline.

	1899																		
	Aug. 2	23	1033	1,044,000	1.21	4,000	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	...	...	
	Aug. 5	25	1038	944,000	1.3	4,500	28.0	3.0	66.0	2.5	0.5	60	20	340	420	++	++	++	
XII.	Aug. 11	19	1030	720,000	1.42	4,750	17.2	0.4	78.8	3.0	0.6	85	19	300	385	++	++	++	Died Aug. 15, 1899.
	Oct. 24	32	1035	2,100,000	0.84	8,000	29.0	0.5	68.0	2.0	0.5	16	0	24	40	+	++	+	
	Nov. 10	37	1037	2,020,000	1.00	3,000	17.5	5.5	72.0	5.0	0.0	5	0	10	15	+	++	+	
XIII.	Dec. 6	48	1047	2,348,000	1.12	9,000	24.5	2.0	67.5	5.5	0.5	4	0	4	8	+	+	+	Improvement.
	Sept. 8	25	1034	960,000	1.4	3,000	54.8	1.6	43.6	0.0	0	12	12	12	36	+	++	++	
	Sept. 29	35	1038	1,968,000	0.98	2,009	49.8	0.8	47.8	1.6	0	16	24	32	72	+	++	+	Improvement.
	Oct. 20	42	1045	3,060,000	0.77	2,000	39.5	1.5	55.5	3.5	0	2	0	0	2	0	+	+	"
	Nov. 26	44	1045	2,736,000	0.88	1,500	30.0	6.0	57.0	7.0	0	0	0	3	3	sl	+	+	"
	Dec. 29	50	1046	2,760,000	1.0	2,000	44.0	8.0	45.0	3.0	0	0	0	0	0	0	+	+	"
	1900																		
	Feb. 11	64	1052	3,250,000	1.1	4,000	35.0	5.0	55.5	4.0	0.5	0	0	0	0	0	+	+	"
	Mar. 21	72	1054	3,720,000	1.07	6,000	30.0	6.0	56.0	7.0	1.0	0	0	0	0	0	+	+	"
	May 2	75	.....	4,140,000	0.99	6,500	32.0	4.0	59.0	5.0	0	2	0	0	0	0	sl	sl	"
XIV.	1899																		
	Nov. 3	22	1031	744,000	1.62	1,000	57.0	4.5	38.5	0.0	0	25	5	85	115	+	++	+	
	Nov. 10	22	1031	810,000	1.49	1,500	60.0	2.0	33.0	4.5	0.5	15	0	81	96	+	++	+	
	Nov. 17	20	1033	920,000	1.20	2,000	41.5	5.0	46.5	7.0	0	10	20	60	90	+	++	+	
	Dec. 7	44	1046	2,536,000	0.95	3,000	42.0	3.0	44.0	10.0	1.0	0	0	0	0	0	+	+	Improvement.
	1900																		
	Jan. 1	55	1048	2,800,000	1.08	8,500	16.0	2.6	76.0	5.0	0.4	19	0	51	70	+	++	sl	"
	Jan. 18	62	1052	2,650,000	1.28	6,000	20.0	7.0	65.0	8.0	0	12	0	12	24	0	+	sl	"
	Feb. 23	54	1050	2,400,000	1.23	4,000	32.0	4.0	60.5	3.5	0	4	4	32	40	0	+	sl	"
	Apr. 10	20	.....	1,132,000	0.97	3,500	46.8	0.8	49.0	0.8	2.0	14	0	102	116	sl	++	++	Decline.
	May 8	20	1032	630,000	1.74	1,200	51.0	1.0	46.0	1.0	1.0	12	0	36	48	+	+++	+++	"
XV.	1899														30	+	++	+	
	May 20	32	1037	726,000	2.4	5,000	21.8	5.0	73.0	1.0	0.2	10	0	20					
	Sept. 16	60	1051	3,500,000	0.94	7,000	20.0	0.8	76.4	2.8	0	0	0	0	0	0	sl	sl	Improvement.
	Oct. 11	52	1048	2,088,000	1.32	5.000	29.0	0.5	70.0	1.5	0	0	0	0	0	0	+	+	Decline.
	Dec. 9	26	1034	1,160,000	1.23	1,500	35.2	2.0	60.0	2.0	0.8	6	0	36	42	+	++	++	"
	Dec. 18	22	1033	880,000	1.40	2,000	25.0	1.0	70.0	1.0	1.0	4	0	28	32	+	++	++	"
	1900																		
	Jan. 2	38	1039	1,868,000	1.10	3,000	30.5	2.0	65.0	2.0	1.0	30	0	45	75	+	++	++	Improvement
	Feb. 6	50	1051	2,560,000	1.07	4,500	39.0	1.0	56.0	1.0	0	90	0	180	270	+	++	+	"
	Mar. 11	50	1048	2,240,000	1.10	3,000	20.8	2.8	74.0	2.8	0.4	12	0	36	48	+	++	+	Decline.
	Apr. 17	30	1036	1,568,000	1.6	3,500	40.0	2.0	56.0	0.0	2.0	0	0	70	70	+	++	++	Died May 21, 1900.
XVI.	Jan. 19	15	.....	912,000	0.91	7,200	8.0	12.6	79.0	0.1	0.3	7	0	14	21	+	++	+	
	June 6	19	.....	762,000	0.6	7,000	7.4	4.4	87.7	0.5	0	7	0	14	21	+	++	+	
XVII.	Mar. 28	20	.....	701,200	1.57	4,140	44.8	3.8	50.0	1.0	0.4	8	0	24	32	+	+++	++	Died April 6, 1900.
XVIII.	Apr. 4	20	.....	1,674,000?	0.66	1,140	25.5	3.0	69.0	1.0	1.5	1	0	4	5	+	++	++	
XIX.	Apr. 13	25	.....	156,000	8.9	5,936	39.8	1.6	57.0	1.4	1.2	2	0	24	26	+	++	++	Died June 16, 1900.
	June 19	30	.....	996,000	1.7	3,330	42.0	3.5	53.0	1.5	1.0	0	0	10	10	+	++	++	
XX.	June 1	30	.....	756,000	2.0	3.000	.....	.....	.....	.....	.....	...	...	...	...	...	...	...	
	June 15	26	1035	980,000	1.46	8,000	18.0	0.8	78.4	2.0	0.8	32	128	400	660	++	++	++	

PERNICIOUS ANÆMIA; A STUDY OF ONE HUNDRED AND TEN CASES.

By RICHARD C. CABOT, M.D.,
of Boston.

The diagnosis in these cases rests upon the following evidence:

1. Autopsy (in addition to clinical evidences) . . .	19 cases.
2. Typical symptoms, signs, blood examination, and course, ending in death—no autopsy . . .	60 "
Typical symptoms, signs, blood examination, and course, but not known to be dead (lost sight of) .	19 "
3. Typical symptoms, signs, blood examination, and course, but still alive (recent cases)	12 "
Total	110 cases.

These figures will be further discussed later on, but are given here simply to indicate what is included in the paper. In addition to these 110 cases I have seen 22 others, which I think probably were cases of pernicious anæmia, but in which a full account of the histology of the blood or some other item necessary to diagnosis is lacking.

Etiology. Among my cases there has been a slight preponderance of males: 57 males to 53 females. The majority of the cases have occurred after the fortieth year; in fact, only 28 occurred at an earlier age. I have had no typical cases under nine years of age. I say no typical cases, for though I have known fatal cases of anæmia in younger children, the anæmia has always seemed to me to be of a different type from that occurring in older persons. Sixty-three of these cases occurred between the fortieth and the sixtieth year, 19 were over sixty, 4 over seventy, the oldest being seventy-nine.

All of these cases came from Boston or its vicinity, and almost all professions and walks of life were represented. One fact which surprised me was the occurrence of no less than seven cases in the wives of physicians.

In four cases the symptoms began immediately after parturition or during the previous pregnancy. Of a relationship to the time of the menopause it is difficult to make any accurate statement, since the catamenia always stops when the anæmia begins. Fourteen cases occurred at about the time when the menopause is to be expected. No definite relationship with syphilis or with intestinal parasites could be traced in any case. There was a history of tertian malaria in four, but nothing pointed to its being the cause of the anæmia. Hemorrhage played a part in the symptomatology of thirty-seven cases, but in no case preceded the onset of the other symptoms. The source of hemorrhage in these cases was as follows:

Bowel (including piles)	15
Nose	13
Gums (steady oozing in 2)	12
Stomach	7
Uterus	3
Lungs	2
Skin	2
Ear (1 pint lost on one occasion)	1
Kidney	2

Two cases were complicated by diffuse nephritis. There was no relation to cancer in any. Psychic factors were prominent in three cases. In one of these the patient's symptoms dated from the time when it was her misfortune to witness the suicide of her son.

FREQUENCY. The fact that so many cases came under my personal observation within seven years seems to me to show that the disease is more common than is usually supposed.

SYMPTOMS. On the whole, the most striking thing to me as I look over these cases is the uniformity and monotony of the symptomatology. One case is remarkably like another. Again, I am surprised at the relative freedom from symptoms in many of them. Several times I have had to restrain patients from going to work, although their red corpuscles numbered less than 2,000,000 per c.m. Other patients with blood equally impoverished have told me that they felt almost if not quite well.

The gravity of such symptoms as are present does not seem to be in any way proportional to the impoverishment of the blood. Cases with only half a million corpuscles often feel better than others with a million and a half.

Again, it should be mentioned that pernicious anæmia is compatible with a very fair color in the cheeks. I have had three cases with typical signs and symptoms of pernicious anæmia in whom, from the appearance of the face, one would never have suspected the diagnosis.

The earliest as well as the most frequent of all symptoms is *muscular weakness.* In two cases this was the only complaint when the patient first came under observation. Next to this, the earliest as well as the most frequent complaint was of *pallor,* which in the great majority of cases had the pale yellow cast so often spoken of. This tint, while I do not think it can be held to be peculiar to pernicious anæmia, is certainly a very suggestive symptom; but it is rather the combination of yellow pallor with plumpness in the face which makes us suspect the presence of pernicious anæmia.

Next to these symptoms in the order of frequency is *dyspnœa,* then *gastric symptoms*—nausea or vomiting, which were nearly as common as those last mentioned. It is noteworthy that in fifty-seven cases the vomiting occurred without any antecedent nausea. In this series, as in that previously published,[1] I found it characteristic of the disease that gastric symptoms occur *paroxysmally,* with intervening periods of relatively good digestion. This fact speaks decidedly against the supposition that the changes in the gastric mucous membrane (which are present, no doubt, in many cases) are such as to cause a serious impediment to digestion or absorption. Atrophy of the gastric tubules cannot come and go as the symptoms do.

Lack of appetite was complained of in not more than two-thirds of the cases. One patient said he never could get enough to satisfy his appetite. Swelling of the lower extremities was a fairly constant, although a relatively late symptom. Palpitation was complained of much less than dyspnœa. Physical examination of the heart showed in most cases nothing more than the functional murmurs which we expect in any anæmia. They are usually less marked in pernicious anæmia than in chlorosis. In seventeen cases there was evidence of mitral regurgitation, and in six of these cases an enlargement of the heart was demonstrated.

The condition of the *bowels* was abnormal in the majority of cases. Diarrhœa occurred paroxysmally in 43 cases and constipation in 32.

[1] Boston Medical and Surgical Journal, 1896.

Symptoms referable to the nervous system were as follows: Vertigo was complained of in about half the cases; headache in 34; ringing in the ears in 30; while signs and symptoms suggestive of changes in the spinal cord were present in 31. Difficulty of vision was mentioned in 20 cases.

Retinal examination was made in 36 cases. Of these 15 showed retinal hemorrhage; 21 showed a normal retina.

Enlargement of the *liver* could be demonstrated in 30 cases, and of the *spleen* in 13. About half the cases showed evidence of emaciation, while in the remainder the fat layer was well preserved. Fever occurred in about two-thirds of the cases, ranging from one hundred degrees upward in 23 cases; in 26 the temperature was constantly normal or subnormal. The urine was normal in 53 cases; showed the presence of albumin in 23 cases, with casts in addition in 21. It was usually pale or normal in color; only twice was it dark.

THE BLOOD. There are undoubtedly periods in the course of most cases of pernicious anæmia in which the diagnosis cannot be made by the blood examination alone. The same can be said of malaria. But it is further true that the condition of the blood in a case of pernicious anæmia may vary a great deal from day to day, so that it is unsafe to draw conclusions from a single examination; for example, I have repeatedly failed to find any megaloblasts at the first examination, yet had no difficulty in discovering them a day or two later. Through reliance on the findings of a single examination I have twice made mistakes in diagnosis.

Regarding the characteristics of the blood in the active stages of the disease, I have nothing to add to what I have previously said in other writings;[1] but comparatively little has been written regarding *the condition of the blood during the remissions of the disease.* This I have had an opportunity of observing in many cases, and have noted the following facts:

1. THE COLOR INDEX. When the red corpuscles begin to increase the color index may remain relatively high or even become still higher; but in the majority of cases this is not so. As a rule, in the remissions of the disease the hæmoglobin is relatively low, as in ordinary symptomatic anæmia, and I have seen two cases which, if examined

[1] For summary of blood examination in 110 cases, see next page.

for the first time during the period of remission, would have certainly been mistaken for ordinary chlorosis.

2. THE LEUCOCYTES. Coinciding with the increase in the red cells there is usually a still greater increase in the leucocytes, so that for a time a moderate leucocytosis may be present. This increase is made up very largely of polymorphonuclear neutrophiles, and is due, no doubt, to the increased activity of the marrow through which both red corpuscles and granular leucocytes are multiplied. As the percentage of polymorphonuclear neutrophiles increases the percentage of lymphocytes decreases, and the myelocytes, which are usually present in small percentages during the active stages of the disease, disappear. The number of megaloblasts steadily decreases, and in their place normoblasts appear for a time; later they, too, leave the circulating blood. The size of the individual red cells is sometimes greater during a remission of the disease than at any other time. In one remarkable case the patient, whose symptoms had totally disappeared and who was actively at work as a newspaper correspondent, dropped in to see me one day, apparently in splendid health and spirits. His skin and mucous membranes were ruddy red, his hæmoglobin 100 per cent., yet to my great surprise I found only 2,500,000 red cells to the cubic millimetre. The stained specimens showed the largest red cells which I have ever seen, for the most part perfectly well shaped and natural looking, but averaging 12μ in diameter. This stage is, however, a comparatively short one, and the size of the red corpuscles soon becomes normal or subnormal. The abnormal staining reactions and the oval forms disappear. As a rule, the count of corpuscles does not remain long above 4,000,000, but ranges in the neighborhood of 3,000,000 during the greater part of the remission.

Summary of the conditions found in the blood of 110 cases at the time of the first examination:

a. Red cells numbered:	
From 500,000 to 1,000,000 in	27
" 1,000,000 to 1,500,000 in	45
" 1,500,000 to 2,000,000 in	34
Total cases under 2,000,000	106
From 2,000,000 to 2,500,000 in	4
	110

b. Leucocytes numbered:

Under 1,000	9
1,000 to 3,000	23
3,000 to 5,000	40
5,000 to 7,000	24
7,000 to 10,000	12
10,000 to 13,000	2
	110

c. Hæmoglobin:

Relatively high in	79
Not relatively high	31
	110

d. Average diameter of red cells at time of first examination:

Increased in	89
Not increased in	21
	110

e. Megaloblasts at time of first examination:

Predominate in	87
Later examination, predominate in	20
Only one examination, no megaloblasts	3
	110

f. Lymphocytes

between 20 per cent. and 30 per cent. in	34
" " 30 " " 40 "	34
" " 40 " " 60 "	33
" " 60 " " 80 "	6
" " 80 " " 90 "	3
	110

g. Eosinophiles:

Under 4 per cent.	90
Over 4 per cent.	13
None found	7
	110

h. Myelocytes. Present in 66 cases. Highest percentages:

10 per cent. in	2
9 " "	1
8 " "	2
7 " "	2
	7

DIAGNOSIS. In view of the fact that there are but nineteen autopsies in my series, the question may be raised whether I have not included cases of latent gastric cancer or other disease, of which the

anæmia was but a symptom. My reasons for thinking differently are as follows:

(*a*) In each of the nineteen cases in which an autopsy was obtained the symptoms, the signs, the course of the disease, and the condition of the blood were of a definite and characteristic type, practically identical in every case, and differing in important respects from the conditions seen by me in any one of several hundred cases of well-identified symptomatic anæmia *of equal severity*.

(*b*) For purposes of comparison I have carefully studied symptomatology, course, and the condition of the blood in several hundred cases of anæmia, obviously symptomatic, occurring in the course of æstivo-autumnal malaria, gastric cancer, or nephritis—all of them cases as severe as those included in my present series—that is, all of them showing less than 2,000,000 red cells per cubic millimetre. A very rich material for this study was furnished by the cases of malaria occurring in the soldiers returning from the late war in Cuba. Despite the most careful study of these cases, I have never been able to find any in which the symptoms, signs, course, and the condition of the blood were like those occurring in the nineteen cases of pernicious anæmia with autopsy mentioned above.

The distinctive features in the diagnosis of pernicious anæmia are as follows:

1. A slow, insidious onset without recognizable cause.
2. Remarkable freedom from pain.
3. Striking absence of emaciation (in most cases).
4. The frequent presence of symptoms suggesting disease of the spinal cord.
5. Paroxysmal attacks of diarrhœa and vomiting, occurring without any obvious relation to diet or to treatment, preceded and followed by periods in which digestion and absorption were performed without apparent difficulty.
6. The tendency to great spontaneous improvement in all the symptoms, followed by rapid and inevitable relapse.
7. A reduction in the red corpuscles to a point below 2,000,000 per cubic millimetre, without a corresponding reduction in the hæmoglobin; a reduction in the number of leucocytes, and especially in the number of polymorphonuclear neutrophiles; the presence of large numbers of over-sized, well-stained red corpuscles, some of them con-

taining nuclei (megaloblasts), together with a tendency to abnormal staining relations and to an oval shape in the red corpuscles.

The distinctive feature in the diagnosis of secondary or symptomatic anæmia are:

1. The presence of a well-recognized cause.
2. The steady progress of the symptoms, especially in malignant disease. If gastro-intestinal symptoms are present they seldom improve spontaneously.
3. Emaciation.
4. The blood.

This tissue shows usually a relatively low percentage of hæmoglobin, and the number of leucocytes, and especially of the polymorphonuclear neutrophiles, is apt to be increased, although this is by no means invariable. The size of the individual red cells is usually normal or diminished and their centres strikingly pale. Over-sized red corpuscles may be present and may occasionally contain nuclei; but, as a rule, they are greatly in the minority, and such nucleated red corpuscles as are present are chiefly of the normoblastic type. The tendency to abnormal staining reactions and to an oval shape in the red corpuscles is usually much less marked than in pernicious anæmia.

(*c*) Having established to my own satisfaction the existence of two types of anæmia—the one (pernicious anæmia) on the basis of nineteen autopsies and of a definite type of symptoms and signs occurring in every case; the other (secondary anæmia) recognized by the existence of an obvious cause, according to the action of which the symptoms progressed or ameliorated—it seems to me justifiable to conclude that the other cases of my series, which were clinically identical with the nineteen in which an autopsy was obtained, were cases of pernicious anæmia, and would have shown typical changes at autopsy, had this been obtainable.

Practically, latent gastric cancer with anæmia is the only disease which anyone is likely to confuse with pernicious anæmia. In all such cases which have come under my observation the symptomatology and course, as well as the condition of the blood, has been very different from that of typical pernicious anæmia. It is true that in two cases of typical pernicious anæmia, diagnosed as such by Ehrlich himself, a cancerous nodule the size of a walnut was found in the stomach post-

mortem; but in such cases I see no sufficient reason for believing that the cancer was the cause of the anæmia. Cancerous growths are not usually accompanied by any considerable degree of anæmia until they have reached a considerable size. It seems to me more reasonable to suppose that in Ehrlich's cases the cancerous nodules occurred as a complication and not as the cause of the anæmia. Latent cancerous growths complicating other diseases have been repeatedly found, and no one would consider a case of nephritis or of phthisis due to cancer of the stomach because such a growth was found in the stomach post-mortem.

(*d*) "*A priori* (Askanazy and other writers have said), there cannot be a distinction clinically between pernicious anæmia and secondary anæmia, because there is no distinction in the marrow between normoblast and megaloblast." This is not upheld, however, by later research. Pappenheim's work goes to show that there are two types of blood formation—the fœtal and the adult—with two types of corpuscles, differentiated, not, as Ehrlich supposes, by the fate of their nuclei, nor, as has often been stated, by the size and staining affinities of their nuclei, but chiefly by the size of the whole cell and by the characteristics of the nuclear network. It is practically though not strictly true to say that a megaloblast is an abnormally large red corpuscle with a nucleus of any kind, while a normoblast is a normal-sized red cell with any kind of nucleus. Large, pale nuclei are simply young nuclei.

(*e*) "It is a common mistake to suppose that by pernicious anæmia we mean simply a very severe or fatal anæmia. But pernicious anæmia is not always very severe; there are relatively mild cases which run on for several years and are compatible with a very fair degree of health, although always fatal within six years, so far as my observation goes. On the other hand, a case of secondary or symptomatic anæmia, such as that due to hemorrhage or to malaria, may be rapidly fatal and yet is easily distinguishable by its symptomatology and by the condition of the blood from pernicious anæmia. I have no experience leading me to believe that there is any such condition as "secondary pernicious anæmia."

(*f*) In the initial stages of the disease and during remissions diagnosis may be impossible. The same is, of course, true of many of the best known diseases.

(*g*) The anæmia due to intestinal parasites, especially to the bothriocephalus latus, is entirely indistinguishable from pernicious anæmia. This has been abundantly proved by the magnificent monograph of Schaumann, and if we are to consider bothriocephalus anæmia as *secondary*, as it seems natural to do, we must admit that this particular type of secondary anæmia is absolutely indistinguishable from the so called primary or pernicious anæmia.

A word may here be said regarding the use of the term "primary anæmia," which means to me simply an anæmia of whose cause we are ignorant. None of the causes as yet adduced to explain pernicious anæmia seem to me satisfactory, although I think there is a good deal of evidence for believing that it is due to a poison absorbed from the gastro-intestinal tract and exerting its deleterious effect upon the blood, the heart, the spinal cord, and the gastro-intestinal tract itself. Among these changes I am by no means sure that the anæmia is the most important, and I regard the others as co-ordinate with it rather than as resulting from it. This view is, to my mind, supported by the fact that the severity of the clinical symptoms is not by any means proportional to the degree of blood impoverishment.

COURSE. In 90 cases I have accurate data as to the course and progress of the disease; in the others my records are somewhat defective. Out of these 90 only 20 were progressive. In 70 there was one or more remissions in which great improvement took place, the symptoms for the most part disappearing, the patient's color and blood-count becoming nearly or quite normal. Twenty-one of these were able to return to work, and felt as well as ever.

Although it is well-known that pernicious anæmia is not a progressive disease, but comes upon the patient in successive waves or paroxysms, I think the full significance of these facts has not been realized. But a short time ago I was talking with a member of this Association, who seemed inclined to doubt the diagnosis of a case of pernicious anæmia because the improvement of the case had been so marked and so rapid. I desire, therefore, to emphasize the point that the disease rarely goes on progressively from bad to worse, and should be expected to show one or more waves of great improvement — improvement which for the most part occurs without any relation to treatment, and which treatment has no power to render permanent.

I have thought it of interest to put together the rate of improvement in some of my cases:

In Case VII. of my series the red cells increased from 1,800,000 up to 5,200,000 in fourteen days. In Case XXXIX. the red cells increased from 2,200,000 to 4,000,000 in thirteen days. In Case LVIII. the red cells increased from 1,500,000 to 3,200,000 in twelve days. In Case XCI. the red cells increased from 1,700,000 to 3,000,000 in fourteen days.

Similar observations have been reported by Ehrlich and other observers.

It is quite possible, although I have no figures to prove it, that in the periods of decline the red corpuscles may fall as rapidly as they subsequently rise. This possibility is suggested by the fact that one rarely sees pernicious anæmia in an early stage—that is, until the red corpuscles have fallen below 2,000,000 per cubic millimetre. Only four of my cases showed more than 2,000,000 red corpuscles per cubic millimetre at the time of the first examination of the blood.

Prognosis. Of the seventy cases which I have been able to follow from start to finish the majority have lasted less than two years; only twelve lasted more than three years, and only two more than four years, the longest being five years. The number of relapses varied from two to five or six. It has seemed to me that such relapses were especially apt to occur in the early spring, and I think it is not impossible that a more direct relationship between the progress of the cases and the weather may later be demonstrable. Remissions may occur even after the red cells have fallen as low as half a million per cubic millimetre. In one of my cases the patient went steadily down hill for four months, until he was too weak to leave his bed, and finally became comatose, with convulsions. At this time he was not expected to live through the night, yet he subsequently recovered sufficiently to be able to do light work about his farm. In the active stages of the disease continuous fever may be present, and in two such cases the diagnosis of typhoid was made.

Out of the whole series there has not been one genuine recovery so far as I am aware. Of the twelve who are known to be still alive eight have been under observation only a few months, and are fast going down hill. Of the other four, two have been under observation for two years, one for two and a half, and one for three and a half

years. In the latter case the condition of the blood is now entirely normal, except for a moderate diminution in the hæmoglobin. The patient feels entirely well.

Of the nineteen whom I have lost sight of, the majority were getting rapidly worse when last heard from.

DURATION. Of the seventy-nine cases regarding which I have complete data, including the date of death—

30	lived	less than	1	year	from the	earliest	symptoms.
20	"	"	"	2 years	"	"	"
10	"	from	2 to 3	"			
7	"	"	3 to 4	"			
3	"	"	4 to 5	"			

TREATMENT. Most of these cases received Fowler's solution in gradually increasing doses continued over long periods. In eight of them bone-marrow was used, either alone or with Fowler's solution. In three of them inhalations of oxygen were given. Personally I do not believe that any of these therapeutic agents has any effect on the course of the disease. I have seen great improvement follow each of them, but when the inevitable relapse later took place the use of the same remedies proved unavailing. On the other hand, I have several times seen sudden improvement occur and the blood count become normal when absolutely no medicine was being given. Several times such improvement followed immediately upon or coincided with an attack of diarrhœa, as if the increased intestinal peristalsis had removed from the system substances which were poisoning it. Acting upon this suggestion, I have of late treated several cases with laxatives or purgatives, in the hope of preventing thereby the absorption of poisonous substances from the intestines. As to the results of such treatment I am not yet prepared to speak.

CLINICAL NOTES OF CASES OF PERNICIOUS ANÆMIA.

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THIS paper is intended to be, for the most part, as its title implies, a clinical one. The cases described were studied at the bedside rather than in the laboratory. In their investigation instruments of precision were employed; not so much to determine the numerical relations of histological elements in each individual case as for purposes of diagnosis—in other words, to distinguish the disease pernicious anæmia from other diseases which it may resemble, and especially from latent gastric carcinoma.

In three of the five cases which I now report there were autopsies, and it is to be regretted that no histological studies of the post-mortem specimens were made. For this my responsibility is only indirect, as the examinations were made by the pathologists of the hospital in which the patients died.

CASE I. *Profound anæmia, with all the characteristics of the pernicious type; peripheral neuritis, with paralysis of extensors; bronzing of skin, with freckle-like spots upon its surface. Result fatal.*—Annie McC., aged sixty-four years, native of Ireland, domestic; admitted to Philadelphia Hospital December 29, 1896. Family history excellent. Parents, brothers, and sisters well and strong up to advanced period of life.

History of present illness. The patient was also well and strong, with a good healthy color, until one year ago, when well-marked gastro-intestinal disturbances set in. These consisted of pain after eating, and frequent vomiting, with diarrhœa, which symptoms have persisted in greater or less degree up to the present time. The vomited matters consisted sometimes of the ingested food; at others solely of bile and mucus. In consequence she has lost much in weight, although is far from being "emaciated." During the period mentioned she has lived chiefly on milk, other food aggravating the above-mentioned troubles. There has, however, been almost complete anorexia.

Symptoms on admission. Great weakness and lassitude, shortness of breath, palpitation of the heart and præcordial oppression, with dull aching pain in the epigastrium. Constriction of the waist, as by corsets, insupportable; cannot partake of solid food; but eggs, milk, and water cause little or no distress. A distinct systolic murmur, loudest at the apex, was heard and considered too harsh to be merely hæmic.

I took charge of the ward containing this patient on February 1, 1897, up to which time the blood had not been examined. The intense lemon-tinted pallor was highly suggestive of pernicious anæmia, and this diagnosis was confirmed by the first blood-count, which was made on February 12th.

Number of red cells, 1,050,000 per c.mm.—21 per cent.; hæmoglobin, 25 per cent.; marked poikilocytosis. No estimate of the white cells, either absolute or relative, is recorded in the ward notes.

From this time until the patient's death, on June 23, 1897, the following counts were made:

March 15, 1897. Number of red corpuscles, 500,000; number of white cells, 5200; Hb., 19 per cent.

April 19*th*. Number of red corpuscles, 560,000; Hb., 14 per cent.

May 11*th*. Number of red corpuscles, 938,000; Hb., 36 per cent.; white cells, 3000.

June 18*th*. Number of red corpuscles, 375,000; Hb., 18 per cent.

The eye-ground was examined by Dr. Charles A. Oliver, who reported several hemorrhages scattered over the retina, the larger ones near the periphery.

From the voluminous ward notes of this case it appears that there was marked improvement as regards the digestive disturbances, with, however, occasional inexplicable attacks of diarrhœa and vomiting.

On February 19th the patient began to complain of a tingling sensation and numbness in feet and hands, and on March 3d these pains are recorded as being so severe as to elicit cries of pain.

The following note was made on March 15th: For several days the patient has been complaining of neuralgic pains in the feet and hands and extending up the arms along the nerve trunks, with gradually increasing weakness and numbness, until to-day there is complete paralysis of extensors of hand and the same condition of those of the feet. She is unable to hold any object with either hand. Fowler's solution, which had been administered in doses of 10 to 20 drops for three weeks, stopped, the arsenic being regarded as a possible cause of the paralysis. Opposed to the hypothesis of arsenical neuritis is the fact that no gastro-intestinal disturbance had been excited by the drug (on the contrary, that previously existing had subsided) or any œdema of the face. The patient at this date declared herself better, except as regards the neuritis, than for six weeks previously. Her statements are, however, unreliable, her mind being readily open to suggestions. The blood-count at this date showed but 10 per cent. of red blood-corpuscles.

April 23*d*. At this date a condition of slight general anasarca was noted,

the face being œdematous, especially on the side on which the patient lay, and the hand hanging over the bed on the same side being decidedly swollen.

May 28th. For two or three weeks previous to this date there had been some improvement as regards the general condition, the patient sitting up occasionally, but the paralysis of the extensors remained complete. The following extract is from the ward notes of May 28th:

Watery diarrhœa continues; œdema of the face and hands has entirely disappeared. The skin of the entire surface of the body has grown darker, with many brown patches, like freckles, upon its surface, most marked on the hands and arms.

June 5th. This morning the patient is very weak, and since the disappearance of the œdema (which began to subside about ten days before this date) her emaciation is apparent. Her color is no longer typical of pernicious anæmia; skin is rather of a light-bronze tint; foot-drop still persists, although there is a little more power in its extensor tendons; hands much improved as to movements of extension.

On June 1st this patient passed out of my care, but from the notes it appears that the asthenia was rapidly progressive, and enhanced by rapidly recurring attacks of gastro-intestinal disorder. As above stated, death occurred on June 23, 1897.

The urine was repeatedly examined. On one occasion a trace of albumin was found, and on another a few small granular casts. Its specific gravity varied from 1014 to 1020.

A differential count of the leucocytes was recently made from a specimen of blood from this case by Dr. L. N. Boston, with the following result:

Polynuclear leucocytes	57	per cent.
Large lymphocytes	18	"
Small lymphocytes	20.5	"
Eosinophile cells	4.5	"

In counting, 600 white cells 9 megaloblasts and 15 normoblasts were seen.

The following conditions were found at the autopsy:

Interstitial nephritis, ovarian cyst, multiple uterine fibroid tumors, atheroma of aorta, pericarditis in patches, vegetations in mitral valves, œdema of lungs.

CASE II. *Profound anæmia following repeated epistaxis; characters of the blood as regards number of red corpuscles and percentage of Hb. the same as those of pernicious anæmia; convulsions following transfusion, the giver of the blood being epileptic; continued fever. Death.*—Samuel B., aged seventy years, colored, sent to the Philadelphia Hospital from the House of Correction, February 10, 1897. No history of previous illness except rheumatism until two months ago, when, after a blow on the nose, epistaxis began. This has continued at intervals ever since.

On admission the patient was in a semi-comatose condition. The tongue was thickly coated, the breath offensive, the bowels loose, and the ocular

conjunctiva yellow. A soft systolic murmur was heard over the base of the heart, and a few mucous râles at bases of lungs behind; the respirations were feeble and the heart-sounds distant and muffled. Temperature the morning after admission 102°; pulse 100, soft and compressible; respirations 20.

The first blood count was made February 21st. Number of red cells per c.mm., 1,357,000; number of white cells per c.mm., 5236. The Hb. was not estimated, nor is there any record of a differential count of the white cells.

It should have been stated that epistaxis was present on admission, and was arrested by tamponing the nares.

The condition of the patient steadily deteriorated until March 5th, when I determined to employ transfusion after the method of Brakenridge, of Edinburgh. This consists of the intravenous injection of blood kept fluid by admixture with one-third of its bulk of a 5 per cent. solution of sodium phosphate.

The marked success attendant upon this measure, reported by Brakenridge and Affleck, fully warrants its employment in cases of pernicious anæmia which do not improve under purely medicinal treatment. The entire amount transfused by Brakenridge at one time, or rather by Duncan, who performed the operations, varied from two to six ounces.

The operation was performed by one of my surgical colleagues, Dr. John B. Shober, on March 5th. Six ounces of blood were obtained from a colored man, an epileptic, of about the same age as Samuel B., the patient. The blood was immediately mingled with two ounces of a 6 per cent. solution of sodium phosphate and the mixture injected into the cephalic vein of the right arm under all the usual antiseptic precautions.

During the operation the patient became very restless, with marked dyspnœa, and perspired profusely. About two hours after the operation his nose began to bleed, and also the wound in the bend of the arm where the transfusion was made.

March 6th. Passed a bad night; pulse frequent and feeble, beating at the rate of 140 most of the time. The temperature, which at the time of the transfusion and for weeks previously had reached 102° in the evening, rapidly fell until at 11 P.M. of the 6th it reached 96°. After that it rose as rapidly until on the evening of the 8th it reached 102.8°. It then resumed its former course until the patient's death, on April 16, 1897.

The general condition of the patient began to improve on March 10th, up to which time he had been in a semi-comatose condition, with muttering delirium, feeble, rapid pulse, and almost inaudible heart-sounds. The treatment during this period consisted largely of the hypodermatic administration of strychnine in doses of one-twentieth of a grain.

15th. Had a good night and was bright and cheerful in the morning. During the day he had three convulsions, each lasting but a few seconds and attended with unconsciousness. The spasm was limited to the muscles of the face, which was drawn toward the right side. On the 17th he bit his

tongue during one of these spasms, which still remained limited to the right facial muscles. After this date the convulsions did not recur. Those convulsive attacks excited considerable comment on the part of those who were familiar with the case, on account of the remarkable coincidence, if it is nothing more, that the giver of the blood transfused into the veins of the patient was an epileptic.

31*st*. The blood was examined to-day, with the following result: Red corpuscles 660,000 per c.mm.; hæmoglobin, 17 per cent.; white cells 3600 per c.mm.

Death occurred on April 16, 1897.

An autopsy was performed, of which the following notes were made: Tuberculosis (?) of mesentery and retroperitoneal glands. Emphysema of left lung. Effusion into both pleural sacs and into the pericardium. Old pleural adhesions in right side. Chronic interstitial nephritis. Splenization of bone-marrow.

Exception may be taken to my regarding this case as one of pernicious anæmia, on the ground that the illness began with, and was kept up by, loss of blood. The characters of the blood were, however, those of pernicious not those of post-hemorrhagic anæmia. This is especially shown by the figures of the last count, which gave 13 per cent. of red cells and 17 per cent. of hæmoglobin.

In post-hemorrhagic anæmia the percentage of hæmoglobin is, as a rule, decidedly lower than that of the red cells,[1] and, in addition, there is not only a relative but an absolute hyperleucocytosis. In the case of Samuel B. the number of the white cells was absolutely diminished. The splenization of the marrow of the long bones is also corroborative of the diagnosis of pernicious anæmia.

A differential count of the blood cells recently made by Dr. L. N. Boston gave the following result:

Polynuclear leucocytes	48	per cent.
Large lymphocytes	37	"
Small lymphocytes	12	"
Eosinophile cells	3	"

In counting, 600 white cells, 3 megaloblasts and 7 normoblasts were seen.

CASE III. *Extreme anæmia with percentage of color higher than that of number; marked gastro-intestinal disorder; great improvement under the use of arsenic and orexine.*—Andrew F., aged forty-two years; laborer; admitted January 23, 1898.

Family history good, both parents living to advanced age, one dying at

[1] See chart in "Die Anæmie," by Lazarus, in Nothnagel's Specielle Pathologie und Therapie.

eighty-five, the other at seventy-two. One brother died from accident, another still living; a sister died from typhoid fever.

Up to April, 1897, the only illness of any moment experienced by the patient was typhoid fever, with which he was attacked when twelve years old. In April last he had an attack similar to the present one, characterized subjectively by great prostration and dizziness, and objectively by extreme pallor.

The present illness began four weeks ago at Sparrow's Point, near Baltimore. The first symptoms were chilly sensations, lasting more than a week, followed by painful throbbing of the head. Two weeks before the chills began it was noticed that he was becoming extremely pale. The appetite has been very poor, the bowels regular, and there has been cough with slight expectoration.

On admission he appeared much older than his age—forty-two years. His pallor was extreme, and the mucous membrane milky white. Vessels at base of neck pulsated strongly. Pulse frequent, quick, and soft.

Lungs yield normal signs except in right infraclavicular region, which is slightly dull, and over which there is slightly increased vocal resonance. Apex beat of heart not visible, but palpable in fifth intercostal space in nipple line. Soft, blowing, systolic murmur at apex. Liver not enlarged. Area of splenic dulness slightly increased. Deep reflexes very slight. Digestion much disturbed; anorexia marked; vomiting induced by slight exertion, such as getting out of bed.

Eye-ground examined by Dr. Charles A. Oliver, February 3, 1898: "Well-marked neuroretinitis, with both deep-seated and superficial hemorrhages in retina and optic nerve, most marked in right eye."

The urine was examined on several occasions and found free from albumin and sugar.

The blood was examined on January 25th, two days after admission:

Number of red corpuscles, 884,000 = 17.6 per cent.; hæmoglobin, 25 per cent.; white cells, 8500. Marked poikilocytosis.

January 31, 1898. Second blood-count:

Number of red corpuscles, 792,000; white cells, 8620.

March 18*th*. Number of red corpuscles, 2,520,000 = 50 per cent.; hæmoglobin, 65 per cent.; white cells, 2986.

At one of the blood examinations a stained specimen showed nucleated red cells with karyokinetic figures.

During the first three weeks of this patient's stay in the hospital no improvement was manifest. His appetite continued very poor and his stomach very irritable, with daily vomiting. Up to this time he had been taking Fowler's solution in gradually increasing doses up to ten minims. He was now given orexine (gr. ij t. i. d.), and coincidently with its administration the appetite and digestion began to improve, and soon became almost voracious. On February 23d it is recorded in the ward notes that he ate for his dinner four small chops, two potatoes, one egg, three slices of

bread and a glass of milk. The increase in appetite may have been a mere coincidence, for I have since given orexine in cases of pernicious anæmia without any apparent influence upon the appetite.

The patient was discharged on April 7th greatly improved, and, according to his own account, as well as he had been for years. His blood-corpuscles, however, at the time numbered less than 3,000,000 per c.mm.

With reference to this last point—*i. e.*, a state of well-being with 50 or 60 per cent. of the normal number of red cells—it would seem that in some cases of pernicious anæmia the possible maximum blood count is a low one. I have seen several cases in which patients with about 2,500,000 red corpuscles per c. mm. (*i. e.*, 50 per cent. of what is considered normal) declared themselves perfectly well and presented all the external signs of health. In one of the cases of this kind the patient, a man of high intelligence, being discouraged by the reports of the blood examinations, and finding himself in excellent condition, refused to have them continued, although he persisted in the use of the therapeutic measures from which he had derived so much benefit.

CASE IV. *Under observation six years, during which there have been several slight and two severe relapses, chronic gastro-intestinal catarrh, with marked exacerbations preceding and during the relapses; complete restoration to health.*—W. P. O., aged fifty-six years, male. This patient, an active and prosperous business man, a contractor, has been under my observation since February, 1894, when I first saw him in consultation with Dr. L. D. Judd. At that time his anæmia was extreme, and his general condition apparently hopeless. In the course of a few months his health was completely restored; in fact, his general condition became better than ever before. During the last six years he has had several slight and two severe relapses, the latter in the spring of 1898 and the autumn of 1899 respectively.

The clinical history is taken almost verbatim from notes furnished me by the patient himself: "February 19, 1894. Complying with your request I will endeavor to repeat in writing the verbal report which I gave you on the occasion of your first visit. I was afflicted with a severe spell of the grip the first year of its appearance here (1889–90), coupled with a stubborn bronchial cold, and, although I became quite strong again and active, I have always since felt that I did not entirely recover from its effects. The latter part of July, 1892, I had some very important work to do in a very limited time at ——— (in the neighborhood of Philadelphia), and spent at least three hours there each day, anxious in mind and tired in body. I accomplished the work a little ahead of time, but it resulted in, or at least ended with, a severe and protracted spell of diarrhœa. I had been subject to similar but shorter attacks for several years. After completing the work referred

to, the entire business was thrown upon me for about two weeks, during which the diarrhœa continued. I was relieved on August 19th and sailed for Boston, hoping to recuperate on the New England coast. The sea trip was very hot, and I suffered severely. I returned the next day, took to bed and remained there for at least two months, being unable to take nourishment without experiencing great distress. Toward the first of the year 1893, I was able to get down town for a short time each day, but did not improve satisfactorily. Early in February I contracted a cold which resulted in an attack of erysipelas, which lasted about two weeks. My convalescence was rapid; the condition of my stomach improved, and I was able to take cod-liver oil. Under its use I gained in flesh until in the spring of that year I weighed 138 pounds, about eight pounds more than I had weighed for a number of years. During six weeks of the summer of 1893 I was at Canandaigua Lake, but, owing possibly to indiscretions in diet, the diarrhœa returned and my health again became worse. It was still further impaired by the fatigue incident to a visit to the Chicago Exposition. During the fall my health and strength steadily deteriorated until I reached the condition in which you found me in February, 1894."

When I first saw this man, on February 3, 1894, he was ghastly pale, gaunt, and emaciated; in short, presented the appearance of an advanced case of pernicious anæmia. The diagnosis was confirmed by the negative results of a thorough physical examination and by an examination of the blood:

Number of red corpuscles per c.mm., 1,237,500; poikilocytosis marked; numerous microcytes; hæmoglobin, 30 per cent.; white cells not increased in number.

At this time he weighed 118 pounds.

His symptoms at this time, apart from the sense of great muscular weakness and dyspnœa on slight exertion, were those of gastro-intestinal disorder. There was great uneasiness after eating, borborygmi, gaseous eructations, and abdominal distention. The urine was free from albumin and casts.

The treatment instituted on February 3d consisted of five grains of naphthalin in capsules thrice daily before meals, and three drops of Fowler's solution immediately after meals. He had a good appetite and was prone to over-indulge it. The diet was, therefore, carefully regulated and restricted. It was composed of chicken, fish, chops, eggs, rice, mashed or baked potatoes, and boiled or roast onions, of which he was very fond. He was also allowed farinaceous food in the form of mush, hominy, and oatmeal.

The dose of Fowler's solution was gradually increased until on February 22d he was taking eight drops thrice daily. Calomel in fractional grain doses was also given at frequent intervals to regulate the bowels. A few days after the naphthalin was ordered he complained of the after-taste of the drug, and bismuth salicylate in five-grain doses thrice daily was substituted. These substances were ordered with a view to intestinal antisepsis. He also took two drachms of cod-liver oil twice daily.

On February 22d he weighed 128 pounds—a gain of ten pounds in less than three weeks.

March 12, 1894. Number of red corpuscles = 2,762,500 (52 per cent.); hæmoglobin = 50 per cent.; poikilocytosis still marked.

Patient has just returned from a week's stay at Atlantic City, and looks and feels much stronger. Dispenses with his carriage in going to business, preferring the cars. Complains of slight looseness of the bowels. He has been taking ten grains of Fowler's solution thrice daily for the last two weeks. This was ordered to be stopped. Is to continue with the bismuth salicylate, which he has also been taking steadily.

April 2, 1894. Number of red corpuscles, 4,000,000; corpuscles still slightly irregular in size and shape, some of them "tailed;" hæmoglobin, 60 per cent.

It is interesting to observe, as I have pointed out in other cases, how, as improvement progresses, the blood, as far as the relative percentages of color and number are concerned, assumes the characters of chlorosis.

23*d*. The patient had just returned from a few days' trout fishing in Monroe County, Pa., and looked the picture of health. In spite of constant outdoor exercise, he had gained four pounds in weight. Number of red corpuscles per c.mm., 4,275,000; hæmoglobin, 70 per cent. Corpuscles much more regular in outline; white cells not estimated, but very scarce.

June 1. Weight 143 pounds, ten pounds more than at any time during the last ten years. Number of red corpuscles, 4,450,000 = 89 per cent.; hæmoglobin, 80 per cent.

In the meantime the treatment previously mentioned had been continued, with occasional intermissions, under the skilful management of Dr. L. D. Judd. The improvement continued during the summer and autumn of 1894, his weight increasing to 145 pounds in summer. No further examinations of the blood were made until February 18, 1895, when I was again consulted. For a few weeks preceding this date the digestive disorders have recurred and the patient's weight has diminished to 132 pounds. The bowels are irregular, constipation alternating with loose motions, and occasionally a mass of mucus is voided per rectum. There is no external evidence of anæmia beyond a slight sallowness of the skin. Number of red corpuscles, 3,130,500 = 62 per cent.; hæmoglobin, 50 per cent. Corpuscles vary greatly in size and shape; no white cells seen while counting the red.

May 23, 1895. Patient has just recovered from an attack of erysipelas. Is very thin, weighing but 120 pounds. Number of red corpuscles, 3,970,000 = 79 per cent.; hæmoglobin, 65 per cent.

September 14*th*. Mr. O. has been in the Pocono Mountains all summer, and is in good condition, having regained his lost weight. The blood was examined at his request. Number of red corpuscles, 3,550,000 = 71 per

cent.; hæmoglobin, 55 per cent. He was surprised at the low figures, which, he said, did not correspond to his sensations. I was rather averse to examining the blood for fear of just such a result.

I did not again see Mr. O. professionally until May, 1898, but was informed that during this long interval he was in good health and actively engaged in business.

May 19, 1898. It is evident that he is suffering from a severe relapse. The skin is of a lemon tint, the lips and palpebral conjunctiva bloodless. Number of red corpuscles per c.mm. 1,800,000 = 36 per cent.; hæmoglobin, 38 per cent. No white cells seen in fields counted, or, in fact, in the entire specimen of diluted blood beneath the microscope. From this relapse he recovered completely.

Another decided relapse occurred during the autumn of 1899. He had been in the city all summer, and hard at work all the time at his office.

October 10, 1899. Number of red corpuscles per c.mm., 1,930,000 (38 per cent.); hæmoglobin, 35 per cent. Under the use of arsenic, intestinal antiseptics, and occasional doses of calomel, with a careful regulation of the diet, improvement soon set in, and in a few weeks he was able to walk a short distance and to take long drives. His blood was not again examined until January 20, 1900, when he came to see me. He looked remarkably well, had resumed his business, and declared that he was, so far as his sensations were concerned, in excellent health. His red corpuscles, however, numbered but 2,700,000 per c.mm., and the hæmoglobin amounted to 50 per cent.

I have made no further examinations of the blood in this case, but I have recently seen the patient, who considers himself in the best of health, and whose general appearance is indicative of vigor and activity.

On three occasions during the last six years I have seen this man apparently rescued from death by the treatment above outlined, and especially by the use of arsenic in doses pushed to the point of tolerance. I need scarcely remind the members of this Association that we are indebted to Prof. Byrom Bramwell, of Edinburgh, for our knowledge of the value of this drug in cases of pernicious anæmia.

CASE V. *Extreme anæmia of less than one year's duration; pleuritic effusion of left side; death from erysipelas.*—William T., aged sixty-two years, white, born in England, by occupation a wireworker; admitted to the Philadelphia Hospital January 25, 1900.

No disease since age of eighteen, when he had typhoid fever. Ten months before admission noticed that in the evening his feet and legs were swollen. Two months later he became decidedly short of breath, and this dyspnœa has been increasing ever since. There is no pain, the appetite is fair, there are no marked digestive disturbances, and the patient sleeps well at night. For many years the man was a heavy drinker, but for the past

year or two has refrained from the use of alcoholic liquors. He is of large frame and well covered with adipose tissue, but ghastly pale, the skin possessing the peculiar lemon tint of pernicious anæmia. Physical examination yielded negative results, except as regards the thorax, which on the left side was flat from the third rib downward in front, and below the spine of the scapula behind. Over this area behind, the breath-sound was distant and bronchial, and the vocal and tactile fremitus completely absent. Two examinations of the blood were made in this case.

January 27th. Number of red corpuscles per c.mm., 1,000,000 (20 per cent.); hæmoglobin, 20 per cent.

February 1st. Number of red corpuscles per c.mm. (average of two counts), 945,000 (19 per cent.); hæmoglobin, 18 per cent.

The corpuscles are irregular in shape, and their average size appears larger than normal. A few nucleated red cells (normoblasts) with deeply staining nuclei observed.

An ophthalmoscopic examination by Dr. Charles A. Oliver revealed "no coarse changes in either eye."

On February 16th the patient, who had been placed upon the use of arsenic, intestinal antiseptics, and orexine, and who was thought to be slightly improving, developed erysipelas, which involved the face and neck, and terminated fatally three days later.

An autopsy was held, of which the following notes are recorded:

"Body well-nourished; extremely anæmic; feet, legs, and thighs œdematous; abdomen containing 7000 c.c. of straw-colored fluid; left pleura contains 2000 c.c. of amber-colored fluid; entire pleura covered with a thick, well-organized membrane; right pleura normal; heart cavities filled with liquid blood; no coagulum anywhere; valves and openings normal; coronaries slightly thickened; heart muscle shows increase of fibroid tissue; left lung is consolidated (from compression) and airless throughout; right lung emphysematous, with small scar at apex; liver pale, its capsule thickened, in a state of fatty infiltration, with slight increase of connective tissue; stomach normal as to size and thickness of walls; a few hemorrhagic spots on its mucous membrane."

The foregoing cases are selected from a number which have come under my observation during the last five or six years, because each of them possesses points of practical interest.

In Case I. there was paralysis of the extensors of the hands and feet, evidently due to peripheral neuritis Whether this neuritis was toxic, induced by arsenic, or not, is an open question. It seems to me, however, that if such were the case peripheral neuritis would be of common occurrence in pernicious anæmia, most cases of which are treated with large doses of this drug. In one of the latest mono-

graphs[1] on pernicious anæmia it is stated that there are no symptoms of importance referable to the peripheral nerves.

In the same case there was bronzing of the skin, which might have been caused by the arsenic exhibited, and in addition there were freckle-like spots scattered over the surface of the integument. In another case, an old man under my care at the Philadelphia Hospital a few years ago, the entire surface of the body was covered with spots precisely resembling freckles, but the skin was not bronzed.

In Case II. the occurrence of convulsions after transfusion with blood from an epileptic has been already alluded to. If these convulsions had occurred immediately after the operation of transfusion they might have been reasonably attributed to the circulatory disturbance to which it gave rise. As, however, they did not take place until ten days after the transfusion, the coincidence of convulsions in the giver and receiver of the blood seems to me to possess remarkable interest.

In Case III. improvement coincided with return of appetite, which seemed to be excited and maintained by orexine. It is only proper to add, however, that I have employed orexine to stimulate the appetite in other cases, and in vain.

Case IV. is remarkable for the success attendant upon the treatment pursued, and illustrates also the notorious tendency of pernicious anæmia to relapse.

Case V., which terminated fatally less than a month after admission, is added, not so much on account of its being a well-marked case of pernicious anæmia as because it illustrates, as does also Case IV., the tendency of the disease to be complicated with erysipelas.

In all five of the cases the blood presented the characters which are universally accepted as those of pernicious anæmia, namely, extreme reduction in the number of red corpuscles and relatively high percentage of hæmoglobin. All other blood changes in this disease, such as poikilocytosis, microcytosis, and the presence of nucleated red cells, large and small, are, from the practical standpoint of diagnosis, of subordinate importance. According to my experience there is no disease, except pernicious anæmia, in which

[1] Die Anämie, von Dr. A. Lazarus, ii. Abtheilung, S. 137.

the number of the red corpuscles is at any time reduced below 20 per cent. of the normal—*i. e.*, below 1,000,000 per c.mm.

The disease with which pernicious anæmia is most apt to be confounded is, undoubtedly, latent gastric cancer. Marked digestive disturbances, extreme cachexia, and sometimes great emaciation are common to both, but the state of the blood, as regards the number of red corpuscles, is widely different in these two affections. As I have said elsewhere,[1] I have never seen a case of gastric cancer in which the number of the red corpuscles was reduced below 30 per cent.—*i. e.*, below 1,500,000 per c.mm., and I have found in the blood of such a case a few days before death 2,760,000 red corpuscles per c. mm.—*i. e.*, 45 per cent. of the normal number, while the percentage of color was but 20. In another case of advanced gastric carcinoma I found 60 per cent. of red corpuscles and 55 per cent. of hæmoglobin ; in still another, 80 per cent. of red corpuscles, and so on. Such figures, in my experience, absolutely exclude pernicious anæmia. I have had under my care at the same time, in the same hospital ward, two cases—the one suffering from pernicious anæmia, the other from gastric cancer. The latter was far weaker than the former, while his red corpuscles were four or five times more numerous. In cancer of the stomach the oligocythæmia does not keep pace with the cachexia ; in pernicious anæmia the cachexia does not keep pace with the oligocythæmia. In this connection I would call attention to the fact that the muscular strength and the powers of endurance are often remarkably well preserved in advanced cases of pernicious anæmia. For example, in the notes of a case which I reported in collaboration with Prof. Osler[2] in 1886, it is recorded that the patient "came to have his blood examined, walking a distance of nearly two miles. Was not fatigued, but complained of slight numbness in the legs." At that time the red corpuscles numbered 1,215,000 per c.mm. (24 per cent.), and the percentage of hæmoglobin was 28. A similar case is recorded by Laache, the patient walking three kilometres, the entire distance being *up hill*, when his blood contained less than 1,000,000 red corpuscles per c.mm.[3]

[1] Archiv für Verdauungskrankheiten, Band iv., Heft 1.
[2] The American Journal of the Medical Sciences, April, 1886.
[3] Die Anämie, S. Laache, 1883, p. 147.

To return to the question of the comparative numbers of the red corpuscles in gastric cancer and pernicious anæmia: In the former disease, when well advanced, in fact up to the point of death, I have found the number of the red corpuscles to range between 2,000,000 and 3,000,000 per c.mm., and sometimes to exceed the latter figure. On the other hand, I have never seen a case of pernicious anæmia in which, before death, the number of the red corpuscles did not fall far below 1,000,000 per c.mm. The comparatively high blood-count of gastric cancer has been observed by others, and is, I presume, generally accepted as a characteristic of the disease. For example, Laache found 3,489,200 red corpuscles per c.mm. (about 70 per cent.) in a case of cancer of stomach and liver less than two months before death;[1] 67 per cent. in another; 43 per cent. in a third, and 57 per cent. in a fourth. Similar figures have been published by Stengel,[2] who found an average hæmic unit of 58 in three advanced cases of gastric carcinoma. Contrast these percentages with 7, 10, and 18, which are those I have frequently found in advanced cases of pernicious anæmia. It is my opinion, as the result of many years' observation, that the differential diagnosis between pernicious anæmia and latent gastric cancer, and consequently the diagnosis of these two diseases, may be more certainly made by a blood-count than by any other method, not excluding a chemical examination of the gastric contents. In fact, the latter may be misleading, as, for example, in cases of pernicious anæmia associated with extensive atrophy of the gastric mucosa. In such cases anacidity, which is a characteristic of gastric cancer, is present, as a matter of course. In the case already referred to, which was reported by Prof. Osler and myself, there was total destruction of the mucous membrane of the stomach. If in that case the stomach contents had been tested for HCl, the result would of necessity have been negative, and, therefore, misleading. The case was studied in 1886, before the importance of anacidity as a symptom of gastric cancer was generally recognized, and, therefore, the diagnosis was based upon the most reliable sign of pernicious anæmia, the reduction of the number of the red corpuscles to about 25 per cent. of the normal.

[1] Loc. cit., p. 63.

[2] Therapeutic Gazette, June, 1894.

I admit the possibility of the reduction of the number of the red corpuscles in gastric cancer to 40 or even to 30 per cent. of the normal—*i. e.*, to figures characteristic of pernicious anæmia, although I have never met with such a condition. Supposing such a case to exist, I would regard it as one of pernicious anæmia complicated with gastric cancer, or as one of gastric cancer complicated with pernicious anæmia, for the figures last mentioned are characteristic of pernicious anæmia and not of gastric cancer.

The relatively high percentage of hæmoglobin, which is so characteristic of the blood of pernicious anæmia, depends upon two, perhaps upon three causes, of which but one is generally recognized: 1. It depends upon the increased average size of the red corpuscles, each one containing more than the normal amount of hæmoglobin. 2. Upon the fact that in some cases there is an unusual number of microcytes, which are so highly colored and so minute that they have been compared to "small, red-tinged fat globules." They are much better seen in a dried smear of blood than in the diluted blood from which the count is made. Whether seen or not, they are not counted, and, therefore, contribute to raise the percentage of color. 3. A high percentage of hæmoglobin may depend upon the time at which the examination of the blood is made. Hunter has called attention to the fact that the exacerbations of the disease coincide with an increased yellowness of the skin, sometimes amounting to icterus, and a deeper color of the urine, the latter being due to the presence of pathological urobilin, and all dependent upon increased hæmolysis. In other words, the icteric tinge of the skin and the deeper hue of the urine are hæmatogenous—*i. e.*, caused by a dissolution of the red blood-corpuscles. Now, if the hæmoglobin is estimated during one of these periods of exacerbations, its percentage will, as a matter of course, be higher than previously or subsequently, since the more highly colored plasma contributes to its elevation. This is a point to which, as far as I am aware, attention has not hitherto been directed.

In conclusion I would reiterate the theory announced by me in 1886,[1] and quoted with approval by the late Prof. Harrison Allen at the Third Triennial Congress of American Physicians and Sur-

[1] Philadelphia Medical Times, April 3, 1886.

geons,[1] that the red blood-corpuscles in pernicious anæmia show marked signs of reversion to the type of blood which is normal in the cold-blooded animals. This theory might be regarded as fanciful if it were based upon a resemblance of the blood of pernicious anæmia to that of the cold-blooded animals (frogs and eels) in any one particular, but the fact is that the red corpuscles of pernicious anæmia resemble those of the said animals in their number, their size, their shape, and the amount of hæmoglobin they carry. In well-marked cases of pernicious anæmia we observe (1) a reduction of the number of the red corpuscles to a degree that is normal in the cold-blooded animals. It is the rule to find in this disease, when well advanced, less than 1,000,000 corpuscles per c.mm. Figures like these are normal in the cold-blooded animals. (2) In pernicious anæmia many of the corpuscles are much increased in size, so much so that they have received the name of megalocytes. Many of them are quite as large as the corpuscles of the lizard and eel. (3) They often show a tendency to assume an oval outline, which is that of the corpuscles of the cold-blooded animals. And (4), finally, to make the resemblance complete, nucleated red corpuscles are commonly present in the blood of pernicious anæmia.

Dr. C. S. Engel, of Berlin,[2] has recently discussed the question whether pernicious anæmia is an example of reversion to the fœtal mode of blood development, and, after an elaborate and minute comparison of fœtal blood in all its stages with the blood of pernicious anæmia, he decides it in the affirmative. Such observations tend to support the view just advanced, for, according to all analogy, the blood-corpuscles of the human embryo in their various stages of development should correspond with those of adult animals on lower planes of evolution.

DISCUSSION.

DR. CABOT: I should like to ask Dr. Henry if in the case that recovered a histological examination of the blood was made.

DR. HENRY: None, except the count and an estimate of color.

[1] Trans. of the Congress of Am. Phys. and Surg., vol. iii. p. 9. "Morphology as a Factor in the Study of Disease."

[2] Virchow's Archiv, Band cliii., S. 537.

DR. CABOT: I see no reason, then, to call it pernicious anæmia. I have had a number of cases of this kind, with recovery, but see no reason to consider them pernicious anæmia.

DR. KINNICUTT: Now that the differentiation of pernicious from other forms of grave anæmia is possible, the prognosis is one of great importance. The rapidity and the degree of improvement with the occurrence of remissions extending over long periods in many cases, had led him to believe that permanent recovery was possible. In a remarkable group of three cases of pernicious anæmia occurring in the same family and under his personal observation, in which the diagnosis had been concurred in by Drs. Janeway, Delafield, and Wm. H. Draper, in one case the remission had even been maintained for three years; in the second there had been one relapse in this period. The third case had terminated fatally in the attack in which his advice first had been sought. The ages of the patients were six, twelve (fatal case), and eighteen respectively.

DR. HARE: There have been several points of interest brought out here. The first one I would speak of is the prevalence of this disease. My experience with the frequency of the disease is that it is much more common than the text-books would have us believe. It has seemed to me more common in those coming from the country than in residents in the city. Without statistics being at hand, it seems to me that the majority of cases that have come under my observation have been from the country districts, and chiefly from the mining regions. I have thought of the possibility of there being a parasitic infection of the gastro-intestinal canal, but have not been able to demonstrate it.

As to the duration, in several cases the patient has lived for a number of years. One man died in my ward but a few days ago who came under observation five years ago, and who five months ago was apparently in perfect health. The singular maintenance of the subcutaneous nutrition is a point of interest which seems to contradict the belief that atrophy of the gastric tubules is a common and important factor.

In regard to what Dr. Cabot said about the use of arsenic, I would like to know why he believes this drug to be useless. Certainly, wonderful improvement takes place under its use, and when we again and again get good results we must attribute it to the drug.

In regard to the suggestion of transfusion, I consider that futile. Many years ago it was demonstrated that the introduction of blood from one person to another always resulted in the death of the red cells. They do not live after the transfusion, and frequently there develops a hæmoglobinuria as a result of the breaking down of the red cells. I want to speak also about another point in which we seem to have been in error. At the present time the medical profession is seeking information about the changes occurring in the blood in disease; but they get little information about the changes which take place in health. The importance of this point has been emphasized by

the researches of Dr. J. K. Mitchell, who has shown that great changes take place in the red cells normally without any impairment of the vitality or health. Reichert and others years ago pointed out the changes which may take place after eating and during sleep, and Dr. Mitchell has shown the changes occurring under massage, after saline infusion, etc., which changes possibly go on in our bodies in health, so that examinations of healthy people made at various periods during the day might show great changes which have not been as perfectly studied as they should be. This is one of the weakest points in our knowledge of the blood changes. It is a constant element of uncertainty in comparing results obtained in healthy and diseased persons. I do not mean that I believe the blood changes found under massage, etc., are dependent upon the development of new cells, but that such influences set them free in the peripheral circulation.

DR. THOMSON: Hunter has recently published a series of ten cases in which he described a disease of the marrow. In these ten cases he found that in nearly all there had been chronic suppuration of the roots of the teeth. Two and a half months ago I was called into consultation in a case occurring in a policeman, and I asked the physician whether he had examined the teeth, and he said "No." So I examined them and found a number of decayed teeth and one bathed in pus. Hunter's view is that the chronic suppurative condition causes the patient to be constantly swallowing different forms of bacteria, and that these may set up an infective process in the gastro-intestinal canal. I think it is worth while to examine into this point.

DR. MCPHEDRAN: Perhaps the most important part of Dr. Cabot's paper is the discussion of the natural history of the disease. In practically no case is the disease a progressive one, but rather characterized by successive periods of improvement followed by relapses. His prognosis is, however, too gloomy, as some undoubted cases recover. During the last few years I have had twenty-two cases under observation; of these at least two have made permanent recoveries. These two were published in the *Medical News* in 1899. One of them was a physician who had all the characteristic symptoms in an extremely marked degree. His recovery was complete within a few months. He has been in active practice ever since. I had a telegram from him on Saturday last, saying that his health continued excellent. The other was a parturient case, and an undoubted one. She continues well.

During the last two years I have been trying the subcutaneous injection of serum. In the first case, an old man who was in a state of muttering delirium, I gave a pint of normal saline every second day, and on the alternate days he had the same quantity by the rectum. He improved rapidly, and on recovering his rational state he refused to continue the subcutaneous injections on account of the pain produced, and the enemata caused diarrhœa. He left the hospital with over 3,000,000 red corpuscles per cubic millimetre and feeling well. He soon relapsed, and died four months later. At the same time I saw an old physician with his son-in-law, also a physician, who

thought the old gentleman so low that further treatment was useless. As normal saline causes so much pain on account of its bulk, I advised him to give blood serum, and, as antidiphtheritic serum was the only one available, we gave it in the hope that it might counteract the toxæmia by stimulation of the lymphoid tissues. About three cubic centimetres were given every second day for two weeks. By that time he was greatly improved. The improvement continued, and in four months he had regained his wonted health, and his blood presented a normal appearance. A year later he became suddenly ill with diarrhœa, and died within two weeks without showing signs of pernicious anæmia. This case might be justly claimed as having made a complete recovery.

At present I have five cases under observation. In three of these I have tried normal animal serum, kindly placed at my disposal by Messrs. Parke, Davis & Co. Its use has not perceptibly affected the blood condition in any of them; in two it produced severe urticaria. In four of them improvement has followed the injection of the antidiphtheritic serum, but they are not yet recovered; however, the serum has not been used long enough to fairly test its efficacy. If it fails I purpose trying antistreptococcus serum.

In only one of these five cases are the teeth and gums not in a healthy condition, although, as is usually the case, they all suffer from stomatitis when the temperature rises or there is nausea and diarrhœa.

Dr. Mitchell: I want to say that all the blood-counts reported here to-day are simply relative and not absolute. If any one of these cases had been subjected to massage the blood-count would have run up considerably. In my own case, and I am reasonably healthy, after one hour's massage the blood-count had risen considerably. This is physiological. If in the frog or the peritoneum of the mouse you regard the circulation under the microscope you see at the diverging loops of minute vessels collections of blood-cells which are very quiet, while past them runs the rapid current of the circulating blood. Every now and then something breaks up one of these groups and the field is clear for a while. Now, it seems probable that something like this is going on in many situations in the human body, and that it is more marked in anæmias than in health, since increase in the blood-count after massage is a great deal larger in proportion in anæmias than in health. It is to be presumed, therefore, that a large number of the cells are out of function, and that when we do something to disturb them by massage or a hot bath we get a great increase in the blood-count.

Dr. Stockton: I wish to mention but one point, and that is the condition of the gastro-intestinal tract in these cases. In the study of twelve cases collected last fall in which I had examined the stomach contents in some during a number of months I came to the conclusion that there is a difference in the gastric secretion in pernicious anæmia from that which occurs in severe secondary anæmias. In the majority of these cases of pernicious anæmia there is distinct failure of the gastric juice, including the disappear-

ance of hydrochloric acid. In certain cases there is a moderate return of the hydrochloric acid during intervals of general improvement. In cases of corresponding severity in secondary anæmia we do not find these changes so marked. I have not seen a case of pernicious anæmia that has not sooner or later showed failure of the gastric juice, and the condition may reach achylia gastrica.

DR. DA COSTA: A few thoughts have occurred to me in regard to the subject under discussion. In the first place, as to the length of the remission. It is sometimes great. I can recall a case of a gentleman who lived a club life—not a dissipated life, but an indolent one—who had a remission of eleven months, and in that time had absolutely no treatment. Then came a relapse in which he died.

In another instance a sailor was in my ward at the Pennsylvania Hospital for four or five months, then went back to sea, having apparently recovered; he took no medicine while at sea, and remained well, but he came back to the hospital in about seven months, the symptoms having returned, and he died in the hospital. These two cases bear upon the length of the remission.

A point, concerning which I have had a different experience from what I understood Dr. Cabot to state, is with reference to the fever. It is, I believe, very common, often continuous, and at times even high. I have been called more than once to see cases of supposed typhoid fever, and found them to be pernicious anæmia. Again, as bearing on this question of fever, it has often occurred to me whether the fever could be made a diagnostic point between this and other blood diseases, and for a time I thought it could; but now I know that in leukæmias we have fever at times, and often in secondary anæmias, and so I believe we must abandon the presence of fever as a diagnostic sign. However, I still think the fever is a more marked symptom in pernicious anæmia than in other blood affections.

DR. HERRICK: Reference has been made to the fact that patients with perhaps only 2,000,000 red corpuscles are symptomatically quite well, and it has seemed to me that the improvement in the symptoms depends largely upon the relative increase in the corpuscles and hæmoglobin. The same thing is seen in chlorosis. We may have a patient with perhaps 30 per cent. of hæmoglobin and push that up to 60 per cent., and the patient regards herself as well. She has relatively 100 per cent. more hæmoglobin than before. It seems to me that the same is true of pernicious anæmia. A patient with 1,000,000 red corpuscles gains 1,000,000 and is much better symptomatically, and regards himself as recovered. Yet we know from the blood-count that he is far from being in a normal condition. The point I wish to emphasize is that it is not so much the absolute increase in hæmoglobin and corpuscles as it is the relative increase that determines the symptomatic or subjective improvement.

DR. CABOT: First, in regard to Dr. Mitchell's point. I was interested in the investigations of Dr. John K. Mitchell at the time they were made, and I

had systematic massage carried out in four of my cases, but, contrary to what Dr. Mitchell has supposed, we found less increase from massage in pernicious anæmia than in the ordinary cases. The change, however, is noted both in health and in anæmias.

The operation of transfusion seems to me unjustifiable, for it is very likely to produce nephritis.

In regard to Fowler's solution, I can only say that in some fifty cases in which it was tried it seemed to me entirely useless. In view of the large number of cases in which there is spontaneous improvement, it is very difficult to draw any conclusions concerning the treatment.

As regards the fever, Dr. Da Costa probably misunderstood me. I quite agree with him concerning that point. There has been fever in the majority of my cases, and it occurs more often in this form of anæmia than in others. In three of my cases typhoid fever had been diagnosed.

In regard to the point referred to by Dr. Hare as to blood-examinations in health, I can say that for eight years now it has been the custom in the Massachusetts Hospital to examine the blood of every patient on the medical side, and in this way we have had material from many thousands of cases which, while not in full health, suffered from diseases not directly connected with the blood. In the vast majority of them the blood varied so little from accepted standards that I see no reason to believe that there are conditions in health where the blood varies any more widely from the figures generally accepted as normal.

DR. HENRY: In regard to my statement as to the number of red blood-corpuscles in gastric cancer, I would say that I simply quote from my own experience. I have never seen a case of pernicious anæmia proceed to a fatal issue without the red corpuscles being reduced below 1,000,000, nor a case of gastric cancer in which they fell below 1,500,000. One of the gentlemen has spoken of atrophy of the stomach as though it were supposed to be commonly the cause of pernicious anæmia. That is not the case; it may be one of its causes.

I would like to ask Dr. Cabot if my case is not a case of pernicious anæmia how he would classify it. It is not secondary to the known causes of anæmia, such as Bright's disease, cancer, etc.; it is not chlorosis; it is not leukæmia. What is it?

DR. CABOT: I should regard it as a case of secondary anæmia of unknown cause.

PRIMARY ECHINOCOCCUS CYSTS OF THE PLEURA.

Report of a Case of Primary Exogenous Echinococcus Cysts of the Pleura, Showing Hyaline Degeneration of the Cuticle without Lamellation, with Notes from the Literature.

By CHARLES CARY, M.D.,

AND

IRVING P. LYON, M.D.,

OF BUFFALO, N. Y.

It has seemed advisable to report in detail the following case of echinococcus cysts of the pleura, both because of the rarity of hydatid disease in America, and especially because of the atypical degeneration of the cyst-walls found in the case obscuring their true nature and causing difficulty in the diagnosis:

Case. *Summary: Physical signs of chronic pleurisy, with adhesions and effusion at right base; aspiration of albuminous fluid loaded with cholesterin crystals; clinical diagnosis of chronic encysted pleural effusion. Operation: Lung free, no adhesions, no effusion; removal from pleural cavity of a small mass of collapsed cysts, resembling closely echinococcus cysts. Microscopical examination: Outer cyst-wall thin, hyaline, without lamellation, and infiltrated with cholesterin crystals; lining membrane degenerated and fatty, and containing much cholesterin, but no scolices or calcareous corpuscles; final discovery, after continued search, of two echinococcus hooklets. Anatomical diagnosis: Degenerated, exogenous, primary echinococcus cysts of pleura.*—J. O., aged thirty-one years, mulatto (mother black, father white), single, a kitchen servant in restaurants, applied for treatment at the dispensary of the University of Buffalo, January 26, 1900, complaining of shortness of breath on exertion, dull pain in the lower right chest, and inflammation of the bladder. The diagnosis of chronic pleurisy with adhesions and effusion was made, and the patient was admitted to the Buffalo General Hospital, February 2, 1900.

Personal History. The patient was born in Virginia and lived in that State until the age of twenty-one, and *had never been outside the United States.* He

had malaria at Newport News, at the age of twenty-one, and typhoid fever at Charlottesville, at twenty-three. About two years ago he had pneumonia, and was in the hospital at Charlottesville from January to April, 1898. In convalescence he developed pleurisy on the right side and was tapped of "about three quarts" of a clear yellow fluid; recovery, except for a "tender feeling" in the lower right chest occasionally on catching cold. In the autumn of 1898, at Washington, D. C., he developed pleurisy on the right side, and "about three quarts of a yellowish fluid containing some white matter was aspirated from the chest." After this he remained well until the autumn of 1899, when a dull, aching pain developed in the lower right chest, with dyspnœa on exertion, requiring him to stop work at about Christmas. About this time also he first noticed that his urine contained considerable white sediment and that his micturition was frequent and was accompanied with pain at the end of the act, which was referred to the glans penis. He denied any history of gonorrhœa, but admitted having had a sore at the age of twenty-five on the penis, which was followed by a blotchy eruption over the body and general bone-aching. He took treatment and recovered. Since his present illness began, about last Christmas, he has lost considerable weight and strength and has been unable to work. He has never had jaundice to his knowledge. In regard to his association with dogs, he said that he always lived with them until he left home at the age of twenty-one, since then he has not had much to do with them.

Condition on Admission. The patient was a small, thin, anæmic, sickly-looking mulatto, weighing 115 pounds. A blotchy pigmentation was observed over both cheeks. Lips and mucous membranes were pale, conjunctivæ clear; finger-tips and nails showed no clubbing or incurvation. Temperature, 98.5° F.; pulse, 78; respiration, 24.

Thorax. On *inspection*, nothing distinctive noted; no bulging; respirations shallow and increased in frequency. On *palpation*, over the lower right chest in the axillary line at the end of deep inspiration was felt a very rough, prolonged, vibrating friction of maximum intensity. Vocal fremitus was diminished over the right base up to the level of the fifth space; above this normal. On *percussion*, there was marked dulness over the right base, rising to the level of the fifth space in the axillary line and sagging somewhat below this level in front and dropping abruptly behind close to the spinal column. The percussion note was not quite flat over the base, though nearly so in the midaxillary line. The upper limit of dulness moved very slightly on change of position. On auscultation over the area of dulness the breath-sounds were not audible, but the spoken voice could be heard faintly. At the end of inspiration a rough, harsh, loud friction sound was heard in the axillary line as high as the fifth space. No râles were heard. The thorax otherwise showed nothing abnormal.

Heart. Point of maximum impulse in the mammillary line in the fifth space; sounds clear.

Liver. Edge could be felt just at the costal margin.

Spleen. Not palpable.

Abdomen. Negative; no tenderness on pressure over flanks or hypogastrium.

Genitalia. Endoscopic examination (kindly made by Dr. E. J. Meyer) showed a stricture of the membranous urethra and superficial ulceration of the prostatic urethra; no growths or cysts in the bladder.

Urine. Specific gravity, 1017, slightly alkaline, considerable albumin, no sugar, considerable pus, and an occasional hyaline cast.

Sputum. [No material from the deeper air-passages could at any time be obtained.]

The *diagnosis* of chronic pleurisy with adhesions and effusion was made, and on February 10th exploratory puncture with a hypodermatic needle was made. *The needle was inserted four times without result in different places over the area of dulness, but on the fifth puncture, in the sixth space in the anterior axillary line, the syringe filled with fluid,* which was of a straw-yellow color, and opalescent on agitation. It was found to contain a large number of cholesterin crystals, a considerable amount of albumin, and a trace of sugar. Tubercle bacilli were not found.

The large amount of cholesterin crystals in the fluid excited suspicion of old cystic formation, but as no evidence of echinococcus was found the case was assumed to be one of simple chronic, *encysted,* pleural effusion. After a few days, as no improvement had taken place, it was decided to withdraw the fluid by aspiration. On this occasion *the needle was inserted also five times before fluid was obtained,* when about one-half litre of fluid of the same character as above described was withdrawn.

A week later dulness was still found over the right base, though less marked than before. Dr. Roswell Park saw the case at this time and suggested the possibility of hydatid cyst. The patient remained unimproved, and it was decided to open the supposed encysted cavity and produce its obliteration.

Operation. Operation was performed by Dr. Roswell Park, on February 24th. Before incising the chest-wall a small syringeful of fluid was aspirated from the right base on the first puncture. This fluid was in every way similar to the fluid previously aspirated. The chest-wall was then opened and several ribs were resected. The costal pleura was found considerably thickened. After entering the pleural cavity, to our surprise, the lung was seen to be free from adhesions, and no encysted cavity or fluid was found. The lung showed on its surface several small, round, opaque, nodular spots that suggested calcified tubercles. No fluid could be found, and only about two ounces of bloody fluid could be drained from the chest by turning the patient on the right side. In exploring the pleural cavity with the hand *a soft mass was withdrawn without appreciable resistance,* which was about the size of a lemon and consisted of a mass of collapsed cysts closely united together. No fistula through the diaphragm could be felt. The operation was terminated by placing drainage in the chest cavity.

Subsequent History. The patient rallied well from the primary operation, but his pulse, temperature, and respirations tended to increase with consider-

able irregularity. About one week later his condition grew worse, and a secondary operation was done, enlarging the opening in the chest and cleansing the cavity, which had contracted down to rather small size. Free drainage and irrigation of the cavity were maintained throughout the course of the case. The general condition of the patient tended gradually downward, with high and irregular rate of pulse, temperature, and respiration. During the last week of illness the temperature ranged irregularly between 99° and 104° F., the pulse ran from 120 to 140, and the respirations were from 40 to 52 per minute. The physical signs of pneumonia were not found. The patient died on May 4, 1900, without the development of special symptoms. Autopsy could not be obtained.

Pathological Notes on the Fluid and Cysts. (1) *Fluid.* This was faintly alkaline in reaction, of a straw-yellow color, and was clear except for a distinct opalescence when it was agitated, giving the impression that it contained a suspension of gold dust. Chemically, it contained a fair amount of albumin (coagulation by heat, potassium ferrocyanide, biuret tests, etc.) and a faint trace of grape-sugar (Fehling's test). Sodium chloride was not present in excess. Tests for succinic acid and bile pigments were negative. Microscopically, the fluid showed (*a*) *cholesterin* crystals in very large number, (*b*) occasional red blood-corpuscles (from the puncture, undoubtedly), (*c*) a few degenerated fatty cells, without nuclei, and (*d*) a few round, colorless bodies (4–18μ), resembling crystals that did not dissolve or effervesce on the addition of HCl. No echinococcus scolices, hooklets, calcareous corpuscles, or laminated cyst-membrane could be found in a search continued many days. The three specimens of fluid aspirated at different times were all similar in every respect. The specific gravity of the second specimen was 1026.

(2) *Cysts.* The mass removed from the pleural cavity at operation consisted of a small mass of collapsed cysts, closely adherent to one another, and varying in size from that of a millet-seed to that of a small lemon. The different cysts were, in general, easily separated by gentle traction, though some were so closely united that they could not be separated without rupturing their walls. Many of the cysts were found to spring from the walls of adjoining cysts, having a wall in common at their line of union. In the largest cyst, extending inward from its outer wall, were seen two or three small cysts, giving the appearance of daughter-cysts, but no free daughter-cysts were found. The number of individual cysts was not counted, but appeared to be approximately forty. Externally the cyst-walls looked very thin and delicate, white, translucent, and glistened with the impregnation of crystals. When cut, the cyst-wall showed no tendency to curl. The interior of the cysts showed a relatively thick, soft, white, granular layer, which could be removed by the slightest touch. The cysts were all collapsed and without fluid content. When placed in water the cysts absorbed it and swelled to a globular form.

The *microscopic examination* of the fresh cysts showed as follows: (*a*) The *external wall*, when teased, showed no true lamination, though slight sugges-

tions of it were seen in occasional bands of fibrils. No cell structure could be made out. The tissue looked hyaline and structureless. Abundant cholesterin crystals were seen throughout. Treatment with dilute acetic acid and potassium hydrate solution did not modify essentially the appearance. Frozen sections, stained with hæmatoxylin and eosin, showed the same hyaline appearance, with many bands or striations branching off toward the interior of the cyst. On the surface an occasional degenerated cell nucleus was seen, but no true organized cellular membrane. (*b*) The *soft material lining the cysts* was found to consist chiefly of fatty detritus and cholesterin crystals. There were many degenerated fatty cells, without nuclei, which stained well with Sudan III. An occasional small, round, colorless, crystalline body was also seen, which did not dissolve or effervesce in dilute HCl. An exhaustive search, lasting for many days, for echinococcus scolices, hooklets, or calcareous corpuscles was without reward for our labor, but Dr. Stiles, to whom specimens were submitted (see below), was more fortunate in his examination, and succeeded in finding in the cyst contents two *echinococcus hooklets.*

Sections of the cysts hardened in alcohol and formalin offered no evidence not obtained from the frozen sections. The histological examination of the walls of the small daughter-cysts protruding toward the interior of the largest cyst showed exactly the same structure as found in the larger external cysts, except that the few cells and nuclear fragments found at the periphery of the outer walls of the external cysts were not found over the walls of the daughter-cysts.

Believing, as we did, after a careful study of the case, that we were dealing with an atypical and rare form of degenerated echinococcus cysts, and before we had obtained conclusive support of our diagnosis, we submitted specimens of the fresh cysts and also stained sections of them to Prof. William H. Welch, of Baltimore, and to Dr. Charles Wardell Stiles, Zoölogist of the Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C. for their expert opinion. Extracts from their reports are here given, with their kind permission, as follows:

Reports of Prof. William H. Welch.

"I have examined the sections of the cysts. I am of the opinion that the cysts are degenerated echinococcus cysts. The gross appearances of the specimens which you showed me were like those of echinococcus cysts. The microscopical characters of the fresh teased material and of sections of the hardened specimens seem to be best explained upon the assumption that the cysts are much degenerated hydatids. Cholesterin crystals and fatty detritus, such as were present in these cysts, are common in degenerated hydatids.

No organized tissue is present in the walls of the cysts. These walls, as shown in the sections, present an outer, thin, hyaline membrane, with irregular inner surface continuous with fragments and shreds of a structureless material which occupies a considerable part of the interior of the cysts on the sections. There are scarcely any intact cells in the sections; here and there a few are attached to the outer wall and a few nuclear fragments are seen in the interior, but there is nothing indicative of suppuration, or of previously organized tissue, nor is there any suggestion of fibrin or inflammatory exudate in the sections.

"As no hooklets can be detected, I have looked carefully for the characteristic lamellation of the cuticular layer of echinococcus cysts. I think that there are suggestions of such lamellation in the parallel striæ occasionally seen in some of the more coherent and hyaline membranous fragments attached to the wall and in the interior of the cysts, but they are not so distinct as to be convincing.

"It is well known that echinococcus cysts may perish and undergo complete disintegration. Davaine, Leuckart, Neisser and others have described such degenerative changes in the dead cysts. In some of these cases nothing but the hooklets remain to establish the diagnosis. Sterile echinococcus cysts occur, and should these undergo similar degeneration, it is evident that not even hooklets would be present to aid in the diagnosis.

"In your case the degeneration has not reached a stage in which the gross appearances of echinococcus cysts have been obliterated, but the characteristic physical and microscopical features do not seem to me reconcilable with any other sort of cysts than much degenerated echinococcus cysts. As already mentioned, the large amount of fatty detritus and of cholesterin crystals within the cysts is in favor of the diagnosis of degenerated hydatids.

"Echinococcus cysts, of course, receive their nourishment from the tissues in which they are embedded, and impairment of this nutrition tends to the production of sterility and degeneration of the cysts. In your case the partial and small attachment of the cysts to the pleural membrane must have favored these results of imperfect nutrition, and in this way I should explain, at least in part, the sterility of the cysts, and their degenerated condition." (April 1, 1900.)

"In my previous letter I did not speak particularly of the outward curling of incised echinococcus cysts. This physical property is well known, and is demonstrable readily in fresh, undegenerated cysts. As it depends upon the integrity of the parasite, it, of course, is likely to disappear after the parasite dies and undergoes degeneration, as certainly occurred in your case, assuming it to be a bladder-worm. It would not be contended, of course, that the absence of this property would exclude the diagnosis of a degenerated echinococcus cyst.

"As I wrote you, I attach more importance in explaining the sterility of the cysts, and the evidence of death and degeneration of the parasite, to the comparatively limited attachment of the cysts to surrounding living struc-

tures, and their consequent feeble nutrition. Most of the instances of pleural echinococci have been of single or few large cysts, firmly attached in their circumference. The topographical relations of the cysts in your case were rather peculiar and unusual." (April 5, 1900.)

REPORT OF DR. CHARLES WARDELL STILES.

"Referring again to your letters of April 5th and 15th, I have this morning made a microscopic examination of the material you sent me, and all doubts have now been removed from my mind regarding the case, for in one preparation I succeeded in finding an *echinococcus* hook. In endeavoring to isolate it and mount it for you I unfortunately lost it and could not again find it.

"As for the interpretation of the cysts which you showed me, you will recall that at the time I examined them they did not make the impression upon me of being hydatid cysts, nor did your microscopic preparations convince me that they were such. They certainly did not look like any echinococcus cysts which I have ever seen before, nor did they behave as such. This, however, was purely a negative opinion, and the evidence both for and against the interpretation appeared to me to be so uncertain that I was inclined to take entirely a neutral position in this regard. I have examined hundreds of specimens of this parasite from various animals, and I believe this is the first time that I have ever felt in doubt regarding the cyst itself. Finding the hook, however, removes all doubt in my mind relative to the existence at one time of a hydatid cyst in the structure." (April 18, 1900.)

It is seen from the very critical and full reports of Prof. Welch and Dr. Stiles, as well as from the report of our own study of the tissues, above given, that this case was one of unusual pathological interest and rarity, and for this reason we have considered it worthy of a rather full and detailed narration of its study, step by step, through all the difficulties attached to its correct interpretation to its final and definite diagnosis. That the case was one of degeneration of hydatid cysts, we entertained hardly a doubt, after considering all the available evidence, but the proof of this, convincing to others, was not fully in hand until Dr. Stiles' fortunate discovery[1] of a single echinococcus hooklet.

As to the interpretation of the nature and origin of the outer cyst-wall—*i. e.*, whether this thin, hyaline, structureless membrane was derived by a process of degeneration from the cuticular wall of the parasite itself or from the once cellular, fibrous capsule furnished by the surrounding tissues of the host, all doubt seems to be definitely

[1] Dr. Stiles writes that he has since succeeded in finding a second hooklet.

removed by the study of the walls of the small cysts (daughter-cysts) found protruding into the cavity of the largest external cyst. Sections made through that portion of the daughter-cysts which was directed toward the interior of the large cyst showed its wall to be constituted of exactly the same hyaline, structureless membrane which formed the substance of the outer wall of the larger and separate external cysts. The lining membrane also of the internal daughter-cysts was identical in its histological structure with that of the external cysts. The only point of difference found in the finer anatomy between the daughter-cysts and the external cysts was the fact that the former failed to show the occasional degenerated cells and nuclear fragments found at the periphery of the latter. These facts make it clear, we think, that the hyaline, structureless membrane of the outer cyst-walls was derived by a process of degeneration from the cuticle of the parasite itself and not from the tissues of the host.

As Prof. Welch has clearly stated what little is known of the general causes leading to the death and degeneration of the bladder-worm, we need not dwell upon this feature of the case further than to state, more explicitly than we have previously done, the fact that the mass of cysts removed at operation seemed to be attached to the costal pleura in the most delicate manner, by which its removal was effected without appreciable resistance and almost by chance. This loose or partial attachment of the cysts and the churning motion to which they were subjected by the respiratory movements of the lung doubtless determined largely their degeneration.

In reviewing the various cases of echinococcus of the pleura reported in the literature, we have found no mention of a type of degeneration of the cyst-walls similar to that found in our case, nor have we been able to find any reference to such a process of degeneration in the walls of echinococcus cysts from other parts of the body. It is a fact, however, that the reports of cases only occasionally describe the histological structure of the cyst-walls, so that it is possible that the loss of the characteristic lamellation of the outer wall and its degeneration into a thin, structureless, hyaline membrane, *without gross degeneration*, may not be wholly unknown. Such a process, however, must be exceedingly uncommon, else it would have been described in the standard works on helminthology. Dr. Stiles, whose reputation entitles him to recognition as the leading helminthologist

in America, states that he has never before, among hundreds of cases examined, encountered a case in which he was in doubt regarding the cyst itself.

We, therefore, assume that in reporting this case we may, perhaps, be placing on record for the first time the type of degeneration of echinococcus walls, which we have above described. Various other processes of degeneration of echinococci have been described, of which may be stated the following brief summary: The earliest changes usually begin in the surrounding capsule, which softens and disintegrates or, on the other hand, hypertrophies or undergoes calcareous degeneration. This is followed by the fatty degeneration and disintegration of the parenchyma lining the interior of the cyst. The fluid contents of the cyst are gradually absorbed and inspissated into a granular and fatty detritus, or may undergo gelatiniform, colloid, caseous, or purulent degeneration, while the cuticle softens and disintegrates into an amorphous detritus or may become calcified. These processes may also follow the rupture of the cyst. Sometimes the process of degeneration is so complete that there is left only a small, dried-up, knotty mass as the remains of the previous cyst.

The study of the fluid aspirated from the cysts did not assist materially in reaching a diagnosis. Hooklets, scolices, calcareous corpuscles, and bits of cyst-membrane were all absent, and thus spoke against echinococcus fluid. It must be remembered, however, that these structures are found only occasionally in the cyst-fluid, according to Leuckart,[1] "only in a very small minority of the cases of human echinococcus." Hooklets were mentioned in only seven out of the sixty-seven cases of hydatid disease collected by Sommer[2] from the United States. The high specific gravity (1026) of the fluid and its considerable amount of albumin were opposed to the diagnosis of echinococcus. The specific gravity of hydatid fluid ranges usually from 1005 to 1013, and albumin is said by most observers to be absent. Still, instances of high specific gravity and abundant albumin in hydatid fluid are recorded, especially in cases of degenerated hydatids. Cordier,[3] in a case of sterile echinococcus cyst of the liver, found a "serosanguinolent" fluid containing albumin and having a specific gravity

[1] Die Parasiten des Menschen. Aufl. 2, Bd. 1., 1886, Leipzig and Heidelberg.
[2] Echinococcus Disease in the United States. Medical Record, New York, November 23, 1895.
[3] Langsdale's Lancet, Kansas City, April, 1896.

of 1032. Bruce and Sheild,[1] in a case of gelatiniform degeneration of hydatid cysts of the liver, found a gelatinous fluid that was "highly albuminous." Mosler and Peiper[2] have found albumin in such cases of hydatids only as were influenced by a surrounding inflammatory process. Neisser[3] states that after repeated exploratory punctures the fluid may contain albumin. Knaggs[4] found a considerable amount of albumin in the fluid withdrawn from a hydatid cyst by the first puncture. Rosenstein[5] and Jaeger[6] have claimed even that traces of albumin were the rule in hydatid fluid. The presence of succinic acid is regarded as pathognomonic of hydatid fluid, but its absence is of no value as evidence. This acid is said by Leuckart to be "found in hardly any other living organisms." Traces of grape-sugar, as in our case, are usually found. The presence of cholesterin crystals in large amount is certainly suggestive of degenerated hydatids. Still, caution must be enjoined in using this point for diagnosis, for a considerable number of cholesterin crystals may be encountered in fluid from various other cysts and encysted conditions in the body, as we have recently seen in a case of degenerated simple cyst of the testicle, and in a case of colloid carcinoma of the peritoneum. The large amount of cholesterin crystals in the fluid did, however, and correctly, lead us to the opinion that the fluid in the chest was at least encysted, though, as we erroneously supposed, only by inflammatory adhesions and fibrous tissue. Thus, as is seen, the study of the fluid offered little evidence for the diagnosis of hydatid cyst.

We have assumed that the fluid obtained by puncture of the chest cavity came in fact from the cysts. This conclusion could hardly be controverted, we think, after considering the facts above set forth. In this connection it may be worth while to explain the difficulty that was encountered in obtaining fluid by puncture over the area of dulness. On the first occasion the needle had to be inserted five times before fluid was withdrawn, and on the second occasion also five separate punctures were made before fluid was obtained. The very loose attachment of the cysts to the costal pleura and the impregnation of their hyaline walls with crystals of cholesterin forming a

[1] Medico-Chirurgical Transactions, London, 1891-1892, vol. lxxv. pp. 175-188.
[2] Thierische Parasiten. Wien, 1894. [3] Die Echinococcen-Krankheit. Berlin, 1877.
[4] Schmidt's Jahrbücher, clxiv. p. 198.
[5] Die Pathol. und Therap. der Harnkrankheiten. Berlin, 1886.
[6] Meckel's Archiv, Bd. vi.

shield over them, as it were, appear to us to be sufficient to explain this fact.

As the physical examination, symptoms and history of the case offered no evidence of the past or present existence of hydatids in other organs, we have assumed the cysts of the pleura to be primary. *Primary echinococcus cysts of the pleura* are of very rare occurrence, and we have succeeded in finding only thirty-nine cases in the literature.[1] These thirty-nine cases include Neisser's[2] seventeen cases, Madelung's[3] one case, Rosenthal's[4] review of five cases, Maydl's[5] collection of four additional cases, Winzerling's[6] one case (and his two additional cases found in the literature), Mosler's and Peiper's[7] one case, Ascoli's[8] four cases, Vannini's[9] one case, Pasca's[10] one case, Orlandi's[11] one case, and von Bókay's[12] one case. Adding our own case to this enumeration, we have, then, *a total of forty recorded cases of primary echinococcus of the pleura.* Of these forty cases, thirty-two were pleural and eight were peripleural; twenty-four occurred on the right side, eight on the left side, and in eight cases the side was not stated. Echinococci of the pleura secondary to the disease in neighboring organs, especially the liver, are of more frequent occurrence, though still very uncommon.

The exogenous form of echinococcus cysts (*Exôgener echinococcus*, Kuhn), as seen in our case, is relatively uncommon in man, at least in its typical form of multiple, external budding. The endogenous form (*Echinococcus hydatidosus*, Leuckart) and the simple single cysts are the forms usually seen in man. In herbivorous animals the exogenous form is said to be common (Leuckart). A very rare form of the exogenous hydatids is the *Echinococcus racemosus*, Leuckart, which differs from the commoner form of exogenous cysts only in the

[1] This collection of cases does not include the case reported by Dr. D. F. Smith, of Walkerton, Ontario, under the title "A Case of Hydatids of the Lung" (Can. Med. and Surg. Journ., November, 1882, xi., 195-197). The description of this case leads us to believe that it was one probably of primary cyst of the pleura, of the peripleural variety.

Loc. cit.

[3] Beitrage Mecklenbg. Aërzte zur Lehre der Echinokokkenkrankheit. Stuttgart, 1885.

[4] Ueber den Echinococcus der Muskeln. Diss., Berlin, 1888.

[5] Ueber Echinokokkus der Pleura. Wien, 1891.

[6] Ein Beitrage zur Casuistik des primären Pleuraechinococcus. Diss., Jena, 1892.

[7] Loc. cit. [8] La Riforma medica, Napoli, 1894, p. 729.

[9] Bullettino delle Scienze Mediche, Bologna, May, 1896, p. 240.

[10] Bull. del. Soc. Lancis. deg. Osped. di Roma. Anno xvi., Fasc. ii., 1896, p. 84.

[11] Gazz. med. di Torino., 1898, vol. xlix. pp. 501, 521, and 565.

[12] Jacobi's Festschrift, New York, 1900, p. 211.

greater number and smaller size of the cysts, which resemble a bunch of tiny grapes. Indeed, were the individual cysts of our case all small, we might properly describe them as racemose hydatids. No case of multiple, budding, exogenous echinococcus cysts of the pleura has been previously described so far as we have been able to ascertain.

The physical signs found at the base of the right chest in our case were not especially suggestive of echinococcus cysts as opposed to encysted pleural effusion, though no positive, differential, physical signs are known, save the "*fremissement hydatique*," first described by Briançon[1] and Piorry,[2] which could hardly be expected to be obtained in its typical form through the bony chest-wall. It is possible, however, that the prolonged, harsh, vibrating fremitus which we felt and heard over the area of dulness was, in fact, a *modified hydatid fremitus*, produced by the movements imparted to the cysts by the lung in its inspiratory expansion. An irregular line of limitation of the percussion flatness has been said to be usual in hydatid cysts of the pleura, as well as an anomalous mingling of normal and abnormal physical signs on palpation and auscultation. As illustrated by our case, there seems to be little tendency for echinococci of the pleura to invade by extension neighboring organs, excepting in the case of peripleural echinococci, and curiously, also, echinococci of the pleura rarely excite pleurisy.

The prognosis in unoperated hydatid cysts of the pleura, primary and secondary, is almost hopeless, and no remedial measure short of radical extirpatory operation should be considered. Of the thirty-one unoperated cases of primary and secondary echinococci of the pleura in Neisser's statistics, all died without exception, including even those cases in which evacuation took place by rupture into a bronchus. The fatality of unoperated hydatid disease of the pleura is accounted for, in part, by the tendency of the cysts to become infected and purulent, and also in many cases, by the profound *toxæmia* resulting from the rupture of the cysts and the absorption of their fluid, which is very toxic. Brieger[3] first and later also Boinet and Chazovlière[4] have succeeded in separating from hydatid fluid a toxic substance

[1] Essai sur le diagnostic et le traitment des acéphalocystes. Thesis, Paris, August 26, 1828.

[2] De la percussion médiate, et des signes obtenus à l'aide de ce nouveau moyen d'exploration. Paris, 1828.

[3] Langenbuch's Leber-echinococcus und seine Chirurgie, p. 78.

[4] Revue de Médecine, November, 1898, No. 11.

that is rapidly fatal to animals after injection. For the same reason exploratory puncture of the cysts has been followed in many cases by a rapidly developing toxæmia and death, as well as by sepsis. A common sign of toxæmia following exploratory puncture is the development of a general urticarial eruption. Because of the danger of sepsis and toxæmia resulting, it would be conservative practice to undertake a radical operation, following exploratory puncture, at the very earliest possible moment after reaching a diagnosis of echinococcus cyst.

In conclusion, we wish to express to Prof. William H. Welch and Dr. Charles Wardell Stiles our great indebtedness for their interest in our case and their valuable assistance in confirming our diagnosis.

DISCUSSION.

DR. VICKERY: There is difficulty in making a diagnosis of this trouble. I saw a man twenty-five or thirty years of age some time ago presenting symptoms of pleuritic effusion, and on aspiration a puriform fluid was obtained; an operation was done and ordinary drainage instituted without recovery of the patient. On enlarging the opening the surgeon discovered and successfully removed echinococcus cysts. I saw no way of making a diagnosis from the symptoms.

THE POSSIBILITY OF ELIMINATING THE DELETERIOUS WHILE RETAINING THE ANTITOXIC EFFECTS OF ANTITOXIC SERA.

By WILLIAM HALLOCK PARK, M.D.,
OF NEW YORK.

While in the treatment of diphtheria and tetanus we believe that the beneficial effects of antitoxic sera far outweigh the deleterious effects, still all of us would gladly avoid, if possible, the eruptions, the changes in the blood and the constitutional disturbances which occasionally follow the serum injections. These disturbances, occurring mostly in children, and in about 15 per cent. of the cases injected, are, as a rule, simply very disagreeable for the day or two during which they persist. Occasionally, however, they are of more importance, as when, for instance, they occur in a child having severe laryngeal diphtheria accompanied by bronchitis or bronchopneumonia, or in one in poor general condition, the final recovery of the case may be retarded or even prevented. In these cases the primary beneficial antitoxic effects are largely neutralized by the later deleterious effects of the serum. The scarlatinal type of rash is also sometimes very puzzling in a diagnostic way.

In pursuing the investigation of purifying antitoxins it is necessary to learn all that we can of their chemical nature. We find that recent investigations have connected antitoxins and globulins so closely that, as we shall see, we may consider it a probability that the antitoxins are globulins or globulin-like substances. Experiments have apparently demonstrated that whatever precipitates all the globulins from an antitoxic serum precipitates also the antitoxins. This must mean either that antitoxins are precipitated by the same substances as globulins, or that they are without exception completely carried down mechanically by the globulin precipitates.

Certain experiments carried out in the Health Department Laboratories by Atkinson make the mechanical explanation of the bringing down of the antitoxin hard to believe. Thus he found that when a solution of globulin precipitated by magnesium sulphate from a normal or an antitoxic serum was saturated with sodium chloride and gradually warmed to 72° C., there occurred five different precipitates, and in antitoxic sera these precipitates were in each case antitoxic. The filtrate always remained antitoxic so long as any globulin remained in solution, but no longer, so that when the temperature had been raised to 72° C. the last trace of antitoxin as well as globulin had been precipitated.

Now, to have with the rise of temperature, one after another, five absolutely distinct globulin precipitates formed in the saturated sodium chloride solution, and to have each of these carry with it only a portion of the antitoxin, and yet when the fifth and last globulin precipitate had formed to leave absolutely no trace of antitoxin behind in the solution, seems to me difficult to explain on any other supposition than that along with the normal serum globulins there were also antitoxic globulins.

The work of Atkinson, just alluded to, suggested to me an experiment, the outcome of which renders the mechanical theory of the separation of the antitoxin still more improbable. As before, the solution of the precipitate, obtained from antitoxic serum by saturating with magnesium sulphate, was saturated with sodium chloride and heated, but now only to 55° C., so that only that portion of the antitoxin and globulin which is precipitated at the lower temperatures was thrown out. One-half of the filtrate containing still about 30 per cent. of the antitoxin and of the globulins was mixed with the entire globulins from a similar quantity of normal serum from an untreated horse. The mixture of normal and antitoxin globulins saturated with sodium chloride was warmed to 55° C., but here, in spite of a heavy precipitate, only a trace of antitoxin came down, no more than was obtained from the half kept for a control which was heated to the same temperature, but to which no normal unheated antitoxin had been added. If we conceive the globulins in diphtheritic antitoxin sera to be a mixture of non-antitoxic globulins and antitoxic globulins the results of the above experiment would be intelligible. Both globulins would be affected alike by the magnesium sulphate, such

globulin salts being formed that, when put in the saturated sodium chloride solution and warmed, the five precipitates above described would occur. Each would be antitoxic, because in each precipitate would be some non-antitoxic and some antitoxic globulin. It is not meant to affirm that the five separate precipitates indicate exactly five separate globulins, for Atkinson has found that the percentage amount of each precipitate varies somewhat according to the amount of magnesium sulphate present in the saturated sodium chloride solution at the time of heating.

Still another hint of the globulin character of antitoxin is in the remarkable relation which has been found to exist between the globulin amount and the antitoxin amount in the different bleedings during the immunization of the horse to diphtheria toxin. Horse numbered 137 when first obtained contained 3.2 per cent. globulin and three units of antitoxin in each c.c. It is of some interest to note that this is the largest amount of normal antitoxin ever noted by us in any untreated horse. Three months later, after repeated injections of toxin, the globulin, as tested by Atkinson, was 8.2 per cent. and the antitoxin 1200 units per c.c. Three weeks later, toxin injections having in the meantime been omitted, the globulin was 5.9 per cent. and the antitoxin 650 units per c.c. Still ten days later the globulin was 4.7 and the antitoxin 400 units.

During all this time there was no increase in albumin, but a decrease of from 20 to 10 per cent. during the increase of the globulin. This increase and decrease of globulin we have found in all horses to be roughly in proportion to the increase and decrease in antitoxin, and this without any relation to the amount of toxin injected. Figures for many of our horses will appear soon in the *Journal of Experimental Medicine*, in articles by Atkinson and Hiss.

We have then these facts for diphtheria antitoxin. It is present in considerable amounts in the blood of some untreated horses and in large amounts in the blood of immunized horses. The antitoxin in both of these kinds of sera is thrown down with the globulins, and this is apparently a true precipitation and not a mechanical separation. A considerable increase of antitoxin always includes an increase in the total globulins. Diphtheria antitoxin appears, therefore, to be either a globulin or a substance having many of its characteristics.

If this be true, we cannot hope to get a pure antitoxin, but only a

mixture of antitoxin with the normal serum globulin as well as any other substances which are present in the blood and are precipitated by the chemicals which precipitate globulins.

With this idea in view, I asked Mr. Atkinson to saturate a litre of high-grade antitoxic serum, which had unusual rash-producing properties, with magnesium sulphate, and then, after removing all the magnesium sulphate possible by pressing the precipitate between filter papers, to replace the magnesium in the precipitate with sodium. This mixture of globulins and antitoxins and about 10 per cent. of sodium sulphate was then used in 36 cases of diphtheria, with the hope, but hardly the expectation, that in excluding the albumin and the other substances not thrown down by the magnesium sulphate, we might have gotten rid of at least a portion of the deleterious substances of the serum. In all 36 cases of diphtheria were treated, 24 at their homes and 12 in the hospital.

TABLE—Summary of Cases Treated by the Department of Health Inspectors with Diphtheria Antitoxic Globulin.

Inspector.	Cases.	Local rashes.	General rashes.	No. rash per ct.
Dr. Benedict . .	4	2	1	1
Dr. Wootton . .	6	0	0	6
Dr. Somerset . .	7	0	1	6
Dr. Pollitzer . . .	5	0	0	5
Dr. Hubbard . .	1	0	1	0
Dr. Lynde . . .	1	0	0	1
Dr. Lynde, immunized	11	0	0	11
Totals, diphtheria .	24	2	3	19
" immunization	11	0	0	11

Recovered, 23. Died, 1.

The different inspectors sent me the following summaries of their results:

Dr. Benedict writes:

"Marked induration follows its use, which I have never before observed. The induration is painful and occasions discomfort and enforced prostrate position in bed when the buttock is used, a site of injection which has always been my point of injection. The fact that three out of the four cases injected have shown some rash is important, though it is to be considered that the other cases have not received

the same surveillance. I have, however, never seen a case of antitoxin rash before outside of the hospital, and have many times revisited my cases for several days after the original injection.

"In case No. 3, the only serious one in the series, there seems to have been from the globulin just as favorable action as a curative as found in the plain serum. This case was septic, and the nose was plugged, but recovery, which was slow, was uneventful, and began in forty-eight hours after the injection.

"From my experience with this globulin serum, I should not be inclined to use it in outside practice, preferring, for the reasons above, the ordinary serum."

Dr. Wootton writes on his seven cases:

"Rashes occurred in but one case, and this had previously been injected with another serum. As a matter of fact, however, with the exception of a few blotches around the point of injection, rashes were very rare with the serum I had previously used. On the other hand, the swellings at the point of injection seemed to be much more persistent when 'globulin' was used. It is thinner, and, consequently, easier to inject than the other. As to the mortality, the cases seem to me to be too few to draw any conclusions."

Dr. Somerset writes on his seven cases:

"All of the cases recovered. Three of the cases showed irritation at site of injection, resulting in abscess in one of them. One case showed a rash. Of the three cases having local irritations, two were ill-fed and in a miserable physical condition. The results, as regards the lesion and general progress of the cases, do not seem to differ materially from those obtained with the regular variety of antitoxin."

Of the twenty-four cases of diphtheria injected at their homes, most of which were not severe, there was but one death, and that occurred in a baby fifteen months old in which the diagnosis of diphtheria is in doubt, as no diphtheria bacilli were found in the culture.

CASES TREATED AT THE WILLARD PARKER HOSPITAL.

Twelve cases were treated with antitoxic globulin, and twelve others, the cases being taken alternately, were treated with serum of the same bleeding as that from which the globulin was derived. No

rashes appeared in the adults treated with the globulin or with the serum. In the children receiving globulin a little less than 50 per cent. developed scarlatinal rashes; the same was true for the serum cases. As there is a difference of opinion as to whether some of these rashes were due to antitoxin or scarlet fever, I will not give the details of the cases here. I watched them carefully, and am of the opinion that the globulin cases did as well as those treated by the serum, but no better. In a small proportion of cases the globulin with its sodium sulphate caused local pain and swelling, in this respect being less desirable than the untreated serum.

We are, I think, safe in concluding from the clinical observation of the cases treated and from animal experiments, that while the globulin class of substances contains all of the curative bodies of the blood, it also contains to a large extent at least the properties which, in susceptible persons, cause certain changes which are manifested by skin eruptions, usually without but sometimes with fever and other constitutional disturbances. The hope that in separating the globulins and allied substances from the blood we might obtain the protective substances while leaving those that are sometimes harmful, must probably, at least for the present, be given up. We must turn, therefore, to the consideration of other possible methods for eliminating the deleterious properties of the serum.

Several different methods have been advocated to accomplish this, namely, filtration, heating to 58° C., preservation for a considerable period, and more careful selection and treatment of animals used for antitoxin production. Filtration through fairly coarse stone filters, such as the Berkefeld, while removing bacteria and any floating particles, has not, in my experience, succeeded in removing those substances which produce the serum effects. It seems to me, therefore, to be a probability that any filter that allows antitoxins to pass will allow the deleterious substances to pass also.

The heating of serum to 58° C. for twenty minutes has been advocated by Spronck. Used hy him in a large number of cases, such serum gave far less of the "serum effects" than the unheated serum. In a limited experience our results have been about the same from both the heated and the unheated serum.

A number of observers have thought that the rashes, etc., were less from serum kept for some months than from that freshly drawn.

We can certainly affirm that in our experience serum kept for from six months to one year has appeared to be less irritating than when freshly drawn. The difference, however, was not great enough to make us certain that the better results from the kept serum were not accidental. It certainly seems safe to assert, however, that old serum is as good as freshly drawn serum of equal strength in antitoxin. We do not need, therefore, to use freshly drawn serum, but rather serum recently tested for antitoxin strength.

Chemical methods, heat and filtration failing, up to the present, at least, to enable us to retain the antitoxic while lessening or altogether eliminating the deleterious substances, can we through selection of animals, manner of feeding and treatment, improve our present methods of procuring a dispensing antitoxin?

All who have watched the use of antitoxic serum in diphtheria and tetanus obtained from different sources have felt convinced that serums differ in their liability to produce disturbances in those injected. Thus, some time ago, during a whole month at the Willard Parker Hospital there were only two rashes of a mild urticarial type in sixty-five consecutive cases, while another serum produced a rash in twenty of the thirty persons injected.

Such a difference must be attributed to the nature of the serum employed and not to the varying susceptibility of the individuals injected. Not only does the serum from different horses vary, but also different bleedings of the same horse. In selecting our serum we can, therefore, hope to accomplish something.

CONCLUSIONS. Antitoxins are, in all probability, substances having the properties of globulins. They cannot with our present knowledge be separated from that portion of the blood serum which in susceptible persons produces disagreeable effects. The fact, however, that the antitoxic serum from some horses is scarcely at all deleterious, leads us not to give up the attempt of procuring a serum, either by selection of animals or by the treatment of the serum itself, which while being antitoxic will not to any important degree be deleterious. For routine practice at present we can scarcely do better than to follow the general plan of using the serum from all healthy animals which have remained healthy during their period of immunization and which have in their blood a sufficient concentration of antitoxin.

A plan which, with the co-operation of Dr. H. M. Biggs, Director

of the Laboratories, and the Health Commissioners, I am trying to put in effect may possibly prove to be practicable, although it has many difficulties to contend with, and can probably only be carried out by departments of health. Each bleeding of antitoxin gives about three thousand c.c. of serum, which, in the usual strength of three hundred to four hundred units per c.c., suffices for about two hundred patients. The serum from as many bleedings as possible will be used first in ten mild cases which are under the direct supervision of the Department of Health. The serum from any bleeding that gives marked eruptions will be thrown away. The serum from some of the bleedings which seem to be of the very best character will be kept for the most serious cases among those treated at the hospital or by the department at their homes. The remainder of the very good and fairly good serum will be sent out in the usual way. This is rather a small outcome of the work toward bettering antitoxin which we have carried on for some time in the laboratories of the New York Health Department; perhaps in the future others or we ourselves may succeed better.

Finally, I wish to express my thanks to Mr. J. P. Atkinson, the Assistant Chemist, for the use of his globulin determinations in the different antitoxic sera and for his general assistance.

DISCUSSION.

DR. PEABODY: I would like to ask Dr. Park whether in the experience of the Health Board of New York any definite conclusions have been arrived at as to the individual idiosyncrasies in connection with the unpleasant results of the antitoxins—whether a patient who has the skin symptoms on one occasion is likely to have a repetition following a subsequent injection? That individual idiosyncrasy is a matter of importance has been shown in some cases. It has happened to me to divide a single vial between three patients for protective purposes—an infant three years old, the child's mother, and the nurse. The mother and child had no unpleasant symptoms—the nurse was laid up with urticarial fever and joint symptoms, and incapacitated for two weeks. It has seemed to me that this element in the problem is entitled to a great deal of consideration. I think it is more difficult to work up than the purely experimental study in the laboratory.

DR. MELTZER: It would be interesting to know whether Dr. Park has any knowledge of the appearance of rashes even after repeated injections of

antitoxin serum, as it is possible that the human body gradually acquires a certain degree of immunity against these secondary effects of the alien serum.

DR. PARK: As to Dr. Peabody's question, I know of but very few cases that showed liability to rashes and then had after a lapse of time subsequent injections. I remember one case that reacted again.

As to Dr. Meltzer's question: some of the cases have repeated rashes from a single injection, so that in an individual case it is almost impossible to say whether the second rash is due to the original or subsequent injections. Dr. McCullom, at the Boston City Hospital, is using enormous doses of the diphtheric antitoxic serum, averaging about 15,000 units of antitoxin and 45 c.c. of serum to each case, and yet does not note from these enormous doses any appreciable increase in the amount of serum disturbance developed; so it would seem from his as well as my own experience that later injections of serum are not as liable to cause these symptoms as the first injection. An acquired immunity is thus suggested. A small dose of one-half a cubic centimetre is, however, much less apt to cause noticeable disturbances than larger doses of five to ten c.c.

THE BACTERIOLOGY OF HEALTHY ORGANS.

By WILLIAM W. FORD, M.D.,
FELLOW IN PATHOLOGY, MC GILL UNIVERSITY, MONTREAL.

(*From the Molson Pathological Laboratory.*)

SCIENTIFIC literature is full of careful observations of those observers who have studied the various species of bacteria isolated from diseased organs and tissues in man and animals, and scattered in the literature of the past two decades are a few articles which describe the micro-organisms which have been found in the living body where no evident disease was present.

The results of these later observations have been so at variance that practically two schools of bacteriologists have developed: the one studying cultures and smears from healthy organs removed immediately after death, claiming that bacteria are normally found; and the other, using slightly different methods and finding no growth on their cultures from similar organs, attributing the successful results of its opponents to errors in technique, and coming to the conclusion that these organs are normally sterile.

Meissner,[1] early in the last decade, states that "in the living tissues of the healthy animal no bacteria capable of development are present," while Zweifel,[2] quite on the contrary, affirms that in the living tissues bacteria are always present, that, however, they are anaërobic in character, their capability of development thus depending to a larger extent upon the amount of oxygen brought to the tissues by the blood.

Hauser,[3] moreover, following the work of these two men with similar observations, found, almost without exception, that the tissues of the body were sterile, whether sections of these tissues be submitted to bacteriological examinations (Gram's method) or whether cultures be made directly from the organs on the different nutritive media.

Welch,[4] in 1891, speaking with especial reference to the colon bacillus, states that he has isolated this organism from the internal organs of the body only where some distinct lesion of the intestinal mucosæ was present, and almost uniformly failed to find it outside the intestinal tract when no demonstrable lesion of the mucosa existed. He states, moreover, that the colon bacillus does not invade the blood and organs in the process of post-mortem decomposition.*

Among the more extended observations in this particular field of bacteriology are those of Neisser and Opitz, who have not only published the results of their own careful and painstaking researches, but have as well made accurate historical reviews of the bacteriological literature of the past thirty years, especially that portion which deals exclusively with the question under consideration.

Neisser[5] using rabbits and guinea-pigs removed the internal organs (liver, spleen and kidneys, heart, lung, mesentery) with as thorough asepsis as possible, cultivated them for *two days* on nutritive media, and finding that without exception these organs were free from bacteria at the end of this time, concluded that "under normal conditions no bacteria are present in the lymph or blood stream." After feeding different animals with cultures of various micro-organisms, however, and producing distinct lesions of the intestines, he found a large number of internal organs from which bacteria grew, either those with which the animal was treated or those that normally inhabit the intestine.

Opitz[6] removed the mesenteric glands of cattle killed at the abattoir at Breslau, carried them to the Hygienic Institute in the same city, and there, after carefully sterilizing the surface, cut out bits of these glands and cultivated them on agar and gelatin plates. Observing that in the majority of organs thus treated no bacteria grew at the end of *three days*, and that the forms isolated from the organs which decomposed were in all cases spore-bearers, especially the bacillus subtilis, the spores of which are exceedingly hard to kill, he concluded that the mesenteric glands of cattle are normally sterile, that is, that a passage of bacteria through the intestinal wall during digestion normally does not take place.

* Dr. Welch has, however, informed us—and he will, I feel assured, permit me to mention the fact—that in the course of an incompleted research in his laboratory, prior to the commencement of these investigations, it was found that the organs of healthy cats treated immediately after death by the perchloride method (to be described later) gave cultures of more than one form.

Neither Neisser nor Opitz record any observations on organs kept longer than three days, and the latter, in the experiments described above, naturally does not eliminate the possibility of post-mortem changes, as the transportation of the organs from one institution to another, together with the means employed to sterilize the surface, made necessary by such a transportation, consume so much time that rapidly growing species of bacteria might develop, or, on the other hand, bacteria present at the time of death might be destroyed by liberated bactericidal substances; and, to say the least, Opitz is not working with tissues absolutely normal.

For now some years studies more especially on the liver, made by Professor Adami in Montreal, have revealed the presence under the microscope of minute bodies within the cells, present both in diseased states and in organs showing no special lesion, which Dr. Adami could only conclude were of bacterial origin.[7] It thus became of interest to note whether bacteria were taken up by the healthy organism, and Dr. A. G. Nicholls, Senior Demonstrator of Pathology, undertook a study of the bacteriology of the healthy rabbit. His results seemed persistently to show that there was a passage of bacteria into the normal tissues.

Lack of adequate time, however, to carry out an extended series of observations has prevented the completion of enough experiments to determine with sufficient accuracy whether this law holds true for different species of animals under different conditions, and, consequently, the work was elaborated by the Fellow in Pathology.

It is the object of the present paper to describe the experiments made, with more especial reference to the methods employed and the general results obtained than to the particular varieties of organisms isolated.

It was decided to attempt the solution of one part only of this problem, and to determine whether bacteria are normally present in the livers and kidneys of animals killed instantaneously, and not to raise the question of the path of the bacteria from their normal habitation to the organs in which they might be found, a subject which Dr. Nicholls is more especially engaged in studying at the present time.

In addition to the experiments on animals, a number of autopsy cultures were studied, and while a considerable interval of time neces-

sarily elapsed between the moment of death and the moment of making the culture, yet the results of this set of observations seemed so much to verify the work on animals that they have been included in this paper.

It was necessary at the outset to keep two facts especially in mind. First, it was desirable to reproduce the conditions in which the organs normally exist, and to remove them within a time after death, so short that it could be certain that post-mortem changes were not being studied; and, secondly, cultures had to be made on a variety of media both solid and fluid, so as to avoid if possible the common experience of bacteriologists who frequently see bacteria in substances examined and yet are unable to obtain any growth from them.

In this connection may be mentioned the variance in the results of blood cultures obtained by the German and English students as compared with the French, for while the former using solid media, straight or slant, on the surface of which the blood has been smeared, have obtained in many cases no growth on their media, the latter using large quantities of fluid media, especially broth, have found bacteria in a much larger proportion of cases. It may thus be possible that the blood undiluted will exhibit a strong bactericidal power which will be lost if the blood be well diluted, and thus there is frequently a decided growth in broth, for example, as compared with a sterile culture on agar. The same law may hold true for the animal juices as well as for the blood. Therefore, animals were instantaneously killed, the organs were removed with the greatest possible care to avoid contamination; they were then preserved in gelatin, agar, or broth at the room or the body temperature, and cultures were made directly from these organs on both solid and fluid media.

It was decided, moreover, to study animals in both a condition of fasting and of full digestion to determine what changes might be caused by the state of the stomach and intestines, and bearing in mind the negative results obtained by Neisser and Opitz, it was decided to preserve the organs for such a time as to be sure that a small number of bacteria developing slowly in the animal tissues might not escape detection.

The methods employed in this work will be briefly described. The first set of animals was killed early in October of last year. Rabbits were selected, starved for twenty-four hours, killed instantaneously by a

blow on the head, fastened to animal boards and saturated with water, to prevent the hair and fur from flying about the field of operation. The operator's hands were washed with soap and water, soaked in saturated solutions of potassium permanganate and oxalic acid, and then bichloride of mercury solution 1 : 1000 for several minutes.

All instruments were boiled for fifteen to thirty minutes, and with separate instruments for each step of the operation, the skin was removed, a small incision in the abdominal muscles made and the kidneys and half of the liver of each animal were excised, then passed immediately into the gas jet of a Bunsen burner, where they were held in the flame with hot-flamed instruments till the outer surface was scorched or cooked to a grayish-brown. They were then transferred immediately to specially prepared gelatin bottles. These bottles were wide mouthed, furnished with ground-glass stoppers, each perforated by a small opening plugged with cotton, each bottle containing about 50 c.c. of gelatin well sterilized, and the whole placed in the steam sterilizer at a temperature of 110°. At the operation the glass stoppers were removed, the smoking organ dropped directly from the flame into the melted gelatin and the glass stopper immediately replaced. The organs thus removed were preserved at the room temperature for eight days.

Cultures were made from day to day by drawing up a small bit of the organ in a sterile capillary pipette through the perforation in the glass stopper, and inoculating agar and broth-tubes. After eight days the organs were hardened in formal-Müller and sectioned and examined by the carbol-thionin and Gram's method.

From the first six organs thus prepared cultures were obtained on the fourth to the seventh day in four cases, and a similar set of organs was then removed from full-fed rabbits with the same technique and preserved in similar gelatin bottles. Positive results were obtained in four of the six organs of this series.

A third set of rabbits was killed, the organs removed (kidney and liver) with the same care, and I was particular, moreover, to flame the instruments in every case before touching the organs, and to cook the surface of the organ thoroughly in the flame. These organs were preserved in agar in the thermostat at the body temperature.

At the end of three days in this set of cultures the surface of the agar was covered with an abundant growth of bacteria, from which

cultures were made. The organ was then removed, its surface seared by a red-hot knife, and another set of cultures taken from its interior.

The glass-stoppered bottles were now discarded in favor of small two-inch deep Petri dishes half-filled with agar, which could be managed exactly like an ordinary plate culture. Long broth-tubes of larger calibre were also employed, furnished with broken glass in the bottom, having a cruncher of glass rod passed through the cotton-plug, and containing about 100 c.c. of neutral bouillon.

Both agar and broth were sterilized in the autoclave, and at the operation they were opened for only a fraction of a second, and the hot sizzling organ passed directly into the medium.

The organ in the broth was broken up by the glass rod, which was then pulled out through the cotton-plug and the top of the tube was covered with tin-foil. Cultures could be obtained from this as from an ordinary broth-tube.

Thus, in the latter experiments, each set of animals furnished a series of cultures on broth, on the surface of the agar and from the interior of the organ.

As a later procedure the Durham modification of the Smith fermentation-tube was adopted instead of the broth-tube, and glucose broth used instead of the plain. This modification, I may say, consists in having a small test-tube inserted in a larger one, which contains sufficient broth to fill the inner tube.

With the technique and method thus described cultures have been made from the kidneys and liver of full-fed and fasting rabbits, guinea-pigs, cats and dogs, and the various bacteria isolated from them have been identified as far as possible. Especial care has always been taken to avoid contamination. For many of the experiments the instruments had been soaked for some days in a mixture of 40 per cent. formalin* and glycerin, and then boiled immediately before operation; but the surest way of securing their absolute sterility has been to heat them in the flame for several minutes before using.

In all cases the organs have been thoroughly cooked in the flame before preservation. By means of the fermentation-tube the organ preserved in broth has often been found to evolve a considerable quantity of gas, and yet the cultures from it would show only a

* Formalin is 40 per cent. solution of formaldehyde. This antiseptic was originally recommended by Dr. F. Buller.

staphylococcus or a non-gas-producing bacillus. Smears, however, from the original tube would show various bacilli, either the colon or other forms, which were possibly overgrown by the hardier staphylococcus or some variety like mesentericus.

In many cases it has been impossible to identify the organisms isolated, so rudimentary is our knowledge of bacterial species; and while in the earlier experiments careful observations were made to determine if possible which particular variety had grown, a number of different animals being inoculated to establish this point, in the later experiments it has sufficed to describe the bacteria briefly and to separate them into rough types. I hope to describe later the character of the foregoing forms isolated in the course of these experiments.

In work of this kind the chances of contamination are many, and the greatest care must be exercised to avoid this factor. With attention to the details of asepsis, however, the organs may be removed and preserved without introducing bacteria from without into the culture media; but it is a different problem to take routine cultures from these organs from day to day over a period of several days or weeks without at times suspecting that the later growths are due to an earlier contamination. After a certain amount of experience, however, it became possible to take the cultures in the proper way, and a few organs in each series which remained sterile after being tapped for a number of times demonstrated that the bacteria which did grow in the others came from the organs themselves. To illustrate, a liver was preserved for thirty-nine days, cultures taken every third day, and yet at the expiration of this time the cultures were as absolutely free from bacteria as at first. Another organ was preserved for the same time with the same result.

The time of growth of the bacteria followed a fairly general law.

Cultures were usually obtained on the fourth, fifth, or sixth day, at which time the organ would show signs of decomposition. Rarely growths were obtained on the second and third day, but it was usually possible to foretell by the third day what particular organ would furnish a culture, both by means of the discoloration of its surface, its softness where tapped, the color it imparted to the media, and especially by gas evolved in the fermentation-tube.

As a routine measure, therefore, cultures were made every third day; the organs were preserved for fourteen days, those organs being

declared sterile which had not decomposed by this time. Contradictions to this law were frequently noted. In a number of cases there was an abundant gas-production in the broth-tubes, and yet no growth in culture media, while in other cases the organs in agar would present every sign of decomposition, yet no bacteria could be isolated. Cultures taken immediately after removal from the body were invariably sterile, and on the first and second day usually so, though 50 c.c. flasks of bouillon, so useful in blood cultures, were employed.

The results obtained in this work have been appended to this article in tabulated form for convenience of reference, and we may now analyze the various experiments, contrasting the species of bacteria found in the different animals with the different media and under the different conditions of digestion.

The Livers and Kidneys of Rabbits.

The first twelve organs cultivated, which may be comprised in the first set, were taken from fasting and full-fed rabbits and preserved in *gelatin* at the room temperature. From eight of these cultures were obtained, including staphylococci, spore-bearing pathogenic bacilli, varieties of proteus, and a paracolon. The time of growth was often late, sixteenth to seventeenth day, and many of the bacilli were spore-bearers.

Both the late period of development and the character of the bacilli grown might be expected in gelatin cultures at the room temperature. From the four organs remaining sterile, cultures were made at intervals for many days, and yet no growth resulted.

Out of a total of twelve organs eight contained bacteria, a percentage of 66⅔. The same percentage is true of the cultures made.

In the second set, kidneys and livers of rabbits preserved in *agar*, there were fifteen organs cultivated with eighteen cultures. Bacteria were obtained in fifteen of the eighteen cultures—83.3 per cent., while thirteen of the fifteen organs grew—86.6 per cent.

This difference in percentage develops from the fact that two portions of the same liver may be cultivated on different media—for example, in broth and agar, while the kidneys in every case were saved entire. In each series the different parts of the liver have been considered as one organ, while the different kidneys from the same animal necessarily are separate organs, for while the general

conditions governing the lymph and vascular supplies of the two kidneys are identical, yet the bacteriology of the two kidneys of the same animal may be quite different, as has been seen in many cases.

Cultures were obtained from the fasting animals in every case, the growth on the surface of the agar corresponding to that from the organ itself, and, as a rule, with that in the broth-tube. The predominant types are staphylococcus, mesentericus, colon, and paracolon in the fasting animals, while the mesentericus, staphylococcus, subtilis, and proteus grew from the full-fed animals. No culture of colon appeared, however, in the full-fed condition. The percentage of growth in this series is much higher that in any other set of animals, and illustrates possibly a condition of lowered resistance on the part of the rabbits used. They were taken from the laboratory supply which had been kept in confinement in unhygienic conditions for many weeks, and can hardly be said to represent the normal conditions of animals at liberty.

In these cultures the form appearing at the surface is often only one of the forms grown from the organ, as in Series III., Liver II., where a staphylococcus alone appeared on the surface of the agar, and in the organ there grew staphylococcus, mesentericus, and two varieties of paracolon. In Series IV. it may be noted that from Liver I. in both agar and broth the cultures were identical, while the third liver and kidneys were sterile in agar and grew staphylococcus in broth.

A number of cultures were taken immediately in 50 c.c. flasks of bouillon, all of which were sterile except the third kidney, from which grew a mould.

By accident one portion of one liver was preserved without singeing. Its duplicate was preserved in the regular manner; but from both of these organs, and from a part of the organ in broth, the same variety of mesentericus developed.

In general it may be seen that when an organ covered by agar decomposes, only one or two of the forms of bacilli present in the organ grow through the agar to the surface, and that while an organ in agar may not furnish a culture, yet the broth emulsion of another part of the same organ will. Either the breaking up of the organ liberates the bacteria more easily or the broth itself is a better medium for developing an organism. It is possible that the liberation and

neutralization of the bactericidal substances in the juices of the organ may be especially facilitated by a fluid medium.

Livers and Kidneys of Guinea-pigs.

The third set of animals (guinea-pigs), prepared in the usual way, grew practically the same variety of micro-organisms as did the rabbits, except that here the bacillus subtilis appeared in several of the cultures.

Its presence raised immediately the question of the proper preparation of the culture media, but its consistent appearance in cultures on both agar and broth, as in Kidney III., Series V., and its isolation from both the surface of the agar and the interior of the organ, as in Kidney II., Series VI., contraindicated the suspicion that it was an interloper.

A number of sterile organs in this series also pointed to the purity of the culture medium. In the subsequent experiments, however, the Petri dishes of agar were not only sterilized in the autoclave, but tested for a week or more in the thermostat on the suspicion that the spores of the subtilis might have been present in the agar stock.

From twenty-four cultures made here definite results were obtained in eighteen cases—a percentage of 75, while from the actual number of organs cultivated (eighteen) fourteen grew (77.7 per cent.).

Livers and Kidneys of Cats.

The cats next used were more suitable than the rabbits, as they were brought from the country, 150 miles away, kept in confinement for a few days only before operation, and thus represent a thoroughly wild condition. A different variety of organisms resulted from the cultures of this set. Staphylococcus and colon persist, subtilis and mesentericus drop out, and a number of forms like proteus, megatherium, and mycoides appear, as well as a staphylococcus and two varieties of long, narrow, spore-bearing bacilli, whose growth was so slow and weak that a careful study of their characters was impossible. Anaërobic cultures in Buchner jars likewise failed to reveal their identity.

From the twenty-four cultures here made growths were obtained or definite bacteria noted in twenty cases, a percentage of 83.3; fourteen of the eighteen organs contained bacteria (77.7 per cent.).

Livers and Kidneys of Dogs.

In the fifth set of animals the proper conditions were more nearly fulfilled than in any other experiment. The dogs were wild, had been confined only a few days; the technique of operation and the method of making cultures was better understood and handled; there was no doubt of the proper sterilization of the culture media and the Durham-Smith fermentation-tube furnished an accurate means of collecting any gas produced in a decomposing organ, thus indicating the presence of bacteria. The thorough surface cooking which the larger size of the organs permitted, and to which each organ was subjected, left no doubt of the absolute sterility of the surface.

The same flora was isolated as from the cats, especially forms like mycoides, megatherium, B. Zopfii, and many long, spore-bearing bacilli, which could be grouped together like those of the preceding set. The growth of the latter was very scanty, but the microscopical characters of the bacilli were unmistakable. Out of the twenty-four cultures here twenty-one grew (87.5 per cent.), while sixteen of the eighteen organs contained bacteria (88.8 per cent.).

Fœtal Organs.

Four organs at this time were removed from fœtal kittens and cultivated in the same way. Three remained sterile, from one grew a staphylococcus and megatherium, an apparently inexplicable result, yet the four organs were all subjected to the same procedure, especially in the sterilization of the surface.

Sterilization by Perchloride of Mercury.

At the suggestion of Dr. Welch a final set of organs was prepared with a somewhat different method, to see if possible whether any change in the procedure adopted could make any change in the actual results obtained.

Rabbits were killed, the organs were removed carefully, and then placed in dishes of bichloride of mercury 1 : 1000, and left for one hour. The dishes had previously been soaked for from two to eighteen hours in this solution. The organs were left in bichloride an hour, transferred to sterile water, and there left another hour, rinsed off with

boiling hot sterilized water, and placed in fermentation-tubes and sterile Petri dishes, into some of which agar was subsequently poured.

By this method the bichloride of mercury forms an insoluble precipitate of albuminate of mercury on the surface of the organ, which allows complete sterilization of the surface without destruction of the micro-organisms in the interior.

Twenty cultures prepared in this way grew in thirteen cases (65 per cent.), the forms being identical with those from the rabbits originally used, mesentericus, staphylococcus, and colon being more especially present. Of the actual number of organs employed (twelve) nine showed bacteria (75 per cent.).

Examination of Sections of the Organs.

Bacteriological examination of the hardened organs was made in all cases, and the results were somewhat difficult to interpret. In many organs from which bacteria grew the forms isolated could be easily demonstrated in the sections, especially mesentericus and staphylococcus. The bloodvessels, as a rule, were filled by the bacteria. In other cases, however, the only evidence of bacteria was the appearance, under the microscope, of many granules, both extracellular and intracellular, especially in the forms of cocci and diplococci, the numbers of these bodies being relatively great in the organs from which cultures were obtained as compared with a small number of granules seen in sterile organs, and practically none in the fœtal.

The appearance of these bodies was not determined by the variety of bacteria isolated, as they were common to all the organs, whether a staphylococcus, mesentericus, subtilis, or colon was the result of cultivation, and the entire phenomenon suggested the possibility that these granules were broken up, destroyed bacteria.

Results from Autopsies (Man).

The autopsy cultures were made by means of a simple device like a potato-cutter or cork-borer, provided with a piston, which, after sterilization by heat, was pushed through the sterilized surface of the organ, and, when withdrawn, carried with it a portion from the interior of this organ, which was placed in the fermentation-tubes. These cultivations were made some hours after death—four to six hours in the earliest case—and, of course, this element of time de-

tracts somewhat from the accuracy of the results. Twenty-six cultures were made from nine different autopsies, and in every case bacteria were grown from these cultures.

The colon, staphylococcus, and mesentericus were the common forms, together with a number of long, narrow bacilli like those seen in gangrene. No putrefactive organisms were isolated, and from the similar results of early and late cultures one is led to believe that at the time of death a few bacteria were scattered in the organs, which are capable of development and transplantation, rather than that there was a post-mortem passage of bacteria from the intestine, for example, into the organs. In several cases a pure staphylococcus was grown, yet a large quantity of gas was evolved from the original culture, smears made directly, however, showing many bacilli, which might either be the gas-producing colon or some pure anaërobe overgrown by the hardier staphylococcus. Anaërobic cultures in Buchner's jars revealed nothing further to solve this problem.

Conclusions.

There are a number of generalizations which can be made from the scrutiny of the various experiments described above, which both testify to the accuracy of these observations and explain in great part their contradiction of the conclusions of earlier investigators.

A. *Each species of animal showed its own peculiar bacteriology* quite distinct from that of other species, regardless of the conditions in which the animals were killed or in which the cultures were made.

Rabbits. From the kidneys and livers of rabbits there grew mesentericus, staphylococcus, colon, proteus, and a variety of spore-bearing pathogenic bacilli which was not isolated from any other animal. These bacteria were obtained in agar, in gelatin, and in broth, from either full-fed or fasting animals, an interval of several weeks elapsing between the cultivation of each series. The last rabbits were killed over six months after the first, the organs were preserved in a different manner, and yet the cultures were practically identical with those originally seen.

Guinea-pig. The flora from the guinea-pig was similar to that of the rabbits, and yet not identical.

There is not the same profusion of mesentericus as in the other animals, and the bacillus subtilis becomes a quite common form. A

greater number of organs remained sterile. Staphylococci and colon appeared in about the same proportion of the cultures. Both the rabbits and guinea-pigs are herbivora, and their organs show species of bacteria fairly consistent with the food on which such animals live.

Cat. In the organs of the cats there appeared quite different forms, megatherium, mycoides, Zopfii, with an occasional subtilis and mesentericus.

Staphylococci and colon were common, but the prevalent forms were of unknown species grouped about two common types, A and B—long, straight bacilli—spore-bearers, growing with great difficulty on the ordinary media, producing gas in the culture tubes, and isolated from the majority of the organs of this series of animals.

Dog. The forms seen in dogs were similar to those in the cats. There were very few staphylococci, no colon or paracolon, and the spore-bearers of the other carnivora were here replaced by long, narrow bacilli without spores, and by broad, straight bacilli, both gas producers and difficult to cultivate. Mycoides, megatherium, and B. Zopfii continue to grow in many of the cultures.

As a rule, the carnivora, dogs and cats, showed species of bacteria quite similar to each other, yet absolutely different from the cultures obtained from the rabbits and guinea-pigs—herbivora, and these results are thus quite consistent with the difference in the food used by the animals, which would determine to a large extent the intestinal flora.

B. *Each animal used, regardless of its species, showed its distinct bacteriology.* Among the rabbits the second animal of the third series, killed fasting, showed in its organs staphylococcus, mesentericus, paracolon, and proteus, while the third animal showed staphylococcus alone in all its organs.

The first animal of the fourth series showed mesentericus and staphylococcus, while from the third animal nothing grew on agar, and only staphylococcus in broth.

Among the guinea-pigs the second animal of Series VI. showed staphylococcus and colon, while the organs of the third animal were sterile throughout.

There is a corresponding similarity in the cultures obtained in the separate dogs and cats, but possibly the last set of rabbits shows examples of this law more convincing than are seen in any other series.

From the first animal there grew colon or paracolon in every organ, either alone or in combination with other bacilli. The cultures of all of the organs of the second animals were sterile; from the third animal there were cultures from the kidney only; while from the last there was a mixture of colon and staphylococcus.

From two animals, at least, there were no cultures. From five or six there was only staphylococcus in the broth, and from a similar number a single species, like mesentericus, grew from all the organs.

C. *The different organs of the various animals displayed the same bacteria on the different culture media.* Liver I., Series IV., grew mesentericus in both agar and broth, as well as the unsinged liver in agar; Liver I., Series VI., grew paracolon throughout, while Kidney I., Series VII., grew bacillus subtilis on all media.

D. *The different culture media furnished a variation in the species of micro-organisms quite consistent with the growths obtained from the organ itself.* The *surface* of the agar showed frequently one form only, which was isolated later from the organ in combination with other forms, while the broth developed bacteria from organs which were sterile in agar. For example, the surface of the agar in Liver II., Series III., grew staphylococcus alone, but in the organ there appeared paracolons, mesentericus, and staphylococcus. The broth cultures of Liver III. and Kidney III., Series IV., grew a staphylococcus, while the agar cultures were sterile.

It is thus evident that when an organ decomposes, covered by agar, some bacteria develop rapidly and appear on the surface either alone or before the others present in the organs can reach the same position, and it is a significant fact that in practically every organ cultivated in this series of experiments that particular species of bacterium developing on the surface of the agar was obtained later from the singed organ.

The only possible exception to this law is in the case of Kidney I., Series III., where on the surface of the agar a mesentericus appeared, with a staphylococcus, while from the organ a few days later the staphylococcus only grew.

E. *The condition of digestion exerts a decided but not a universal influence* on the species of bacteria isolated from the kidneys and livers cultivated. In many cases the colon group appears in the cultures

from the fasting animals, but fails to do so in the full-fed condition. This is especially well illustrated in Series III. and IV., where the fasting rabbits furnished colon in three out of six organs, while the full-fed rabbits furnished none. The prevalence of the colon group was not marked sufficiently, however, to prove this law in other species of animals, while in the carnivora it was impossible to work out a corresponding law for the unknown bacteria there isolated. The actual number of sterile organs seems to be the same, whether we are dealing with the full fed or fasting.

F. As has already been pointed out, *there was in a number of cases ample microscopic evidence to prove that bacteria had developed in an organ, and yet no cultures could be grown.*

There was a production of gas in several of the Durham-Smith tubes of Series XI., yet no growth on culture media, while the portions of liver of the third animal were discolored, soft and juicy, like those which had furnished a growth of bacteria, and yet the cultures were invariably sterile.

The microscopic examination of these hardened organs showed no bacteria, but the same granular appearance as was noted in the decomposed organs.

The entire number of animals killed was 34, furnishing 93 organs and 122 cultures. Of the 93 organs, 75 furnished definite growths on the various media, a percentage of 80.6. Of the actual number of cultures made, 122, 95 grew, a percentage of 77.8.

This apparent discrepancy is explained when we remember that one portion of an organ may grow on one medium, and a corresponding portion on another medium be sterile, the broth in all cases developing more bacteria than the agar. Each set of animals as well, when analyzed separately, showed over 65 per cent if we consider the different cultures, and over 66 per cent. if we consider the organs. While the highest percentage of organs containing bacteria was 88.6, that of cultures growing was 87.5.

In view of what has already been said, there is some evidence that the total number of organs furnishing cultures is smaller than the number of organs which might actually contain bacteria, as several decomposed organs are marked sterile because no bacteria were grown from them.

Contamination of the cultures may be eliminated for two reasons: The utmost care was taken to remove the organs aseptically and to preserve them in sterile media in sterile dishes. The instruments were thoroughly boiled and flamed, the media were sterilized in the autoclave and then tested, the operator's hands were surgically clean, and in the actual manœuvres care was taken to prevent any possible introduction of bacteria from without. Each organ was either thoroughly singed or soaked in bichloride of mercury to sterilize the surface, and then passed immediately into the culture media prepared for it. The routine cultures were made in the most careful manner possible, and the actual preservation of several organs in the various media, gelatin, agar and broth, for from two to six weeks, and their absolute sterility at the end of this time proves that the laws of bacteriology were carefully adhered to.

Again, *the isolation of different bacteria from different species of animals, from different animals and from different organs, shows that the results of cultivation of these organs depend on actual presence of bacteria in the organs themselves, and not on the accidental introduction of germs from either the air, instruments, the hands of the operator, or the media and dishes used.*

The removal of the organ from the animal the moment after death and its transfer to the culture medium consumed less than five minutes of time, and it is thus certain that these observations represent actual living conditions.

In conclusion, why do these results contradict the results of Neisser and Opitz? The answer to this question is simple. Neisser and Opitz cultivated their organs for two and three days only, and at the end of this time declared their organs sterile. *In my cultivations at the end of three days an identical condition was determined. The cultures were sterile.* There is, then, no doubt thrown upon the facts adduced by these observers. If, however, the organs be left for several days, a week, or two weeks, bacteria will appear on the culture media with such persistence and in such profusion and specific variety as to show that they come from the actual organs and are not introduced from without.

There are two explanations for this phenomenon. On the one hand, the bacteria present in the organs may be so few in number that immediately after death they will not grow on culture media, for

it is now being admitted that to obtain a culture of bacteria in many cases it is necessary to have them present in some slight number. As Haffkine has pointed out, the transfer of bacteria from one medium to another leads to the destruction of a certain number from alteration of environment. Thus where few are present they may all succumb.

On the other hand, the bactericidal substances in the animal juices may be so powerful in the living condition that if they be transferred with bacteria to culture media they will there exert an inhibitory action on these bacteria and render a culture sterile (especially in solid media), whereas, the same juices may lose their bactericidal power if separated from the living animal, as in the case of blood serum, thus allowing the growth and multiplication of any bacteria present in the living organ. This curiously slow development of bacteria within healthy organs removed from the body affords a most interesting problem for further elucidation.

But whatever be the explanation of the facts as a result of the experiments described in this article, it must be concluded that at least 80 per cent. (80.6 per cent.) of the livers and kidneys of healthy normal animals contain bacteria which are capable of development, provided the proper culture media be adopted, and provided that these organs be cultivated for a sufficiently long time after their removal from the animals used.

My thanks are due to Dr. Adami for his great kindness and his unfailing help and advice in this series of experiments.

SET I.

SERIES I.—*Rabbits Fasting. Organs in Gelatin Bottles.*

Rabbit A 1:			
Kidney	I.	Staphylococcus.	8th day.
Liver	I.	Pathogenic spore-bearing bacillus, No. I.	4th day.
Rabbit A 2:			
Kidney	II.	I. Pathogenic spore-bearing bacillus, No. II. II. Paracolon. III. Pathogenic spore-bearing bacillus, No. III.	7th day.
Liver	II.	0	
Rabbit A 3:			
Kidney	III.	0	
Liver	III.	Staphylococcus aureus.	7th day.

SERIES II.—*Rabbits Full Fed. Organs in Gelatin Bottles.*

Rabbit B 1:			
Kidney	I.	Pathogenic spore-bearing bacillus, No. IV.	12th day.
Liver	I.	0	Sterile after 39 days.
Rabbit B 2:			
Kidney	II.	Staphylococcus.	17th day.
Liver	II.	0	Sterile after 39 days.
Rabbit B 3:			
Kidney	III.	Staphylococcus.	4th day.
Liver	III.	Proteus. Paracolon.	16th day.

SET II.

SERIES III.—*Rabbits Killed Fasting. Organs in Agar Bottles in Thermostat.*

		Surface.	Organ.
Rabbit C 1:			
Kidney	I.	Staphylococcus. Mesentericus vulgatus.	Staphylococcus.
Liver	I.	Long spore-bearing bacillus. Paracolon A. Paracolon B.	Staphylococcus. Paracolon A.
Rabbit C 2:			
Kidney	II.	Paracolon C. Mesentericus vulgatus.	Proteus vulgaris. Mesentericus vulgatus. Paracolon B.
Liver	II.	Staphylococcus.	Paracolon. Paracolon B. Mesentericus fuscus. Staphylococcus.
Rabbit C 3:			
Kidney	III.	Staphylococcus.	Staphylococcus.
Liver	III.	Staphylococcus.	Staphylococcus.

Growths obtained on sixth day, previous to which the bottles were unopened.

SERIES IV.—*Rabbits Killed Full Fed. Organs in Agar Plates.*

		Surface.	Organ.	Broth tubes.
Rabbit D 1:				
Kidney	I.	Mesentericus ruber.	Mesentericus vulgatus.	Staphylococcus.
Liver	I.	Mesentericus vulgatus.	Mesentericus vulgatus.	Mesentericus vulgatus. Mesentericus fuscus.
Rabbit D 2:				
Kidney	II.	0	0	Mesentericus fuscus.
Liver	II.	Mesentericus vulgatus. Proteus mirabilis.	Mesentericus vulgatus. Proteus mirabilis.	Mesentericus vulgatus. Bacillus subtilis.
Rabbit D 3:				
Kidney	III.	0	0	Staphylococcus.
Liver	III.	0	0	Staphylococcus.
Liver	I.	Not singed. Mesentericus fuscus. Mesentericus vulgatus.	Mesentericus vulgatus.	

All cultures taken immediately in 50 c.c. bouillon sterile except kidney III., from which grew a mould. Growths obtained fourth to sixth day.

SET III.

SERIES V.—*Guinea-pigs Killed Full Fed. Organs in Agar Plates.*

		Surface.	Organs.
Guinea-pig A 1:			
Kidney	I.	Staphylococcus. Paracolon.	Staphylococcus. Paracolon.
Liver	I.	Mesentericus vulgatus. Bacillus subtilis.	Proteus vulgaris. Mesentericus fuscus.
Guinea-pig A 2:			
Kidney	II.	0	0
Liver	II.	Staphylococcus.	Staphylococcus.
Guinea-pig A 3:			
Kidney	III.	Mesentericus ruber. Bacillus subtilis.	Mesentericus vulgatus. Mesentericus fuscus.
Liver	III.	Bacillus subtilis.	Bacillus subtilis.

Growths obtained at end of seventh day.

SERIES V.—*Guinea-pigs Killed Full Fed. Organs Preserved in Broth-tubes.*

Guinea-pig A 1:			
Kidney	I.	Mould on surface.	
Liver	I.	Not singed.	Staphylococcus.
Liver	I.	Singed.	Staphylococcus.
Guinea-pig A 2:			
Kidney	II.	Mesentericus fuscus.	
Liver	II.	Bacillus subtilis and staphylococcus.	
Guinea-pig A 3:			
Kidney	III.	Bacillus subtilis.	
Liver	III.	0	

Growths obtained at end of seven days.

SERIES VI.—*Guinea-pigs Killed Fasting. Organs in Agar Plates.*

		Surface.	Organ.	Organs in broth-tubes.
Guinea-pig B 1:				
Kidney	I.	0	0	0
Liver	I.	Paracolon.	Paracolon.	Paracolon.
Guinea-pig B 2:				
Kidney	II.	Bacillus subtilis.	Bacillus subtilis.	Staphylococcus.
Liver	II.	0	Staphylococcus.	Staphylococcus.
Guinea-pig B 3:				
Kidney	III.	0	0	Mould.
Liver	III.	0	0	Mould.

Growths obtained at end of seventh day.

SET IV.

SERIES VII.—*Cats Killed Fasting. Organs in Agar Plate.*

		Surface.	Organ.	Broth-tubes.
Cat A 1:				
Kidney	I.	0	Bacillus subtilis.	Bacillus subtilis.
Liver	I.	0	Few spores; no bacilli.	Long bacilli and spores. Variety A.

	Surface.	Organ.	Broth-tubes.
Cat A 2:			
Kidney II.	Proteus. Megatherium.	Proteus. Megatherium.	0
Liver II.	0	Long bacilli and spores. Variety A.	Few long bacilli; no spores. Variety A.
Cat A 3:			
Kidney I I.	0	0	0
Liver III.	0	Mesentericus. Mycoides. Megatherium.	Long, broad, thick bacilli and spores. Variety B.

SERIES VIII.—*Cats Full Fed. Organs Preserved in Agar Plate.*

	Surface.	Organ.	Broth-tubes.
Cat B 1:			
Kidney I.	Mould (mucor) Colon bacilli (?)	Mould. Colon bacillus.	Few bacilli and spores. Variety B.
Liver I.	0	Staphylococcus. Colon.	Few long narrow and few broad bacilli. Variety A.
Cat B 2:			
Kidney II.	0	Few long bacilli. Staphylococcus.	0
Liver II.	0	Few bacilli. Spores. Staphylococcus.	Streptococcus.
Cat B 3:			
Kidney III.	0	Fine bacilli on smear; no growth.	Few long fine bacilli. Variety A.
Liver III.	0	Few bacilli; no growth.	Long straight bacilli; no spores. Variety B.

Gas produced in majority of broth-tubes, which were furnished with inner tubes to collect it. Both Series VII. and Series VIII. anaërobic cultures negative. Growths obtained at end of seven days.

SET V.

SERIES IX.—*Dogs Full Fed. Organs in Agar.*

	Surface.	Organ.	Broth.
Dog A 1:			
Kidney I.	0	0	Long straight bacilli, like Zopfii, short bacilli and large coccoid bodies like staphylococci.
Liver I.	0	Few long straight bacilli.	Few short straight bacilli.
Dog A 2:			
Kidney II.	Mycoides. Megatherium.	Megatherium.	Long bacilli with spores like Zopfii.
Dog A 3:			
Kidney III.	0	Long straight bacilli; no spores.	Few long straight bacilli.
Liver III.	0	Few long straight bacilli.	Long straight bacilli like mycoides, others like megatherium.

Gas produced in all broth-tubes of Series IX.

SERIES X.—*Fasting. Organs in Agar.*

		Surface.	Organ.	Broth.
Dog B 1:				
Kidney	I.	0	Staphylococcus. Mycoides.	Long straight bacilli like mycoides.
Liver	I.	0	Sporelike bodies and long straight bacilli.	Few long and short straight bacilli.
Dog B 2:				
Kidney	II.	0	Staphylococcus.	Spores and long straight bacilli.
Liver	II.	0	Staphylococcus. Mycoides.	Long straight bacilli like mycoides and spores.
Dog B 3:				
Kidney	III.	0	0	Few sporelike bodies and long straight bacilli.
Liver	III.	0	Staphylococcus. Spores. Long straight bacilli.	0

Gas produced in all broth-tubes of Series X. except Liver III.
Growths obtained at end of seventh day.

SET VI.

SERIES XI.—*Rabbits Killed Full Fed.*

Organs removed aseptically; thrown into bichloride of mercury solution 1 : 1000 *for one hour; passed into sterile water for one hour, and then washed with hot sterile water.*

Organs preserved dry in Petri dishes; preserved in agar plates and in broth-tubes.

Rabbit E 1:

Kidney	I.	Dry	=	Short straight bacilli. (Colon?)
Kidney	I.	Broth	=	Short straight bacilli. (Colon?) Large bacilli. (Gas produced.)
Liver	I.	Dry	=	Colon.
Liver	I.	Agar	=	Colon.
Liver	I.	Broth	=	Colon. (Gas produced.)

Rabbit E 2:

Kidney	II.	Dry	=	0
Kidney	II.	Broth	=	0 (Gas produced.)
Liver	II.	Dry	=	0
Liver	II.	Broth	=	0 (Gas produced.)
Liver	II.	Agar	=	0

Rabbit E 3:

Kidney	III.	Dry	=	Colon and heavy thick bacilli.
Kidney	III.	Broth	=	Colon and heavy thick bacilli. (Gas produced.)
Liver	III.	Agar	=	0
Liver	III.	Dry	=	0
Liver	III.	Broth	=	Broad straight bacilli. (Gas produced.)

Rabbit E 4:

Kidney	IV.	Broth	=	Staphylococci and bacilli. (Gas produced.)
Kidney	IV.	Agar	=	Staphylococci.
Liver	IV.	Agar	=	Surface. Mesentericus. Long bacilli-like subtilis. Organ. Mesentericus. Colon-like bacilli.
Liver	IV.	Broth	=	Short and long straight bacilli. (Gas produced.)
Liver	IV.	Agar	=	Long and short thick bacilli.

TOTALS. ANIMALS KILLED.

SET I.

SERIES I. (Rabbits fasting.)		SERIES II. (Rabbits full fed.)	
Kidney I.	+	Kidney I.	+
Liver I.	+	Liver I.	0
Kidney II.	+	Kidney II.	+
Liver II.	0	Liver II.	0
Kidney III.	0	Kidney III.	+
Liver III.	+	Liver III.	+

Number of cultures	12
Number of growths on cultures	8
Percentage	66⅔
Number of organs	12
Number bacteria-containing	8
Percentage	66⅔

SET II.

SERIES III. (Rabbits fasting.)		SERIES IV. (Rabbits full fed.) Agar.		Broth.	
Kidney I.	+	Kidney I.	+	Kidney I.	+
Liver I.	+	Liver I.	+	Liver I.	+
Kidney II.	+	Kidney II.	0	Kidney II.	+
Liver II.	+	Liver II.	+	Liver II.	+
Kidney III.	+	Kidney III.	0	Kidney III.	+
Liver III.	+	Liver III.	0	Liver III.	+

Number of cultures	18
Number of growths on cultures	15
Percentage	83.3
Number of organs cultivated	15
Number of bacteria-containing	13
Percentage	86.2

SET III.

SERIES V. Guinea-pig (full fed). Agar.		Broth.		SERIES VI. Guinea-pig (fasting). Agar.		Broth.	
Kidney I.	+	Kidney I.	+	Kidney I.	0	Kidney I.	0
Liver I.	+	Liver I.	+	Liver I.	+	Liver I.	+
Kidney II.	0	Kidney II.	+	Kidney II.	+	Kidney II.	+
Liver II.	+	Liver II.	+	Liver II.	+	Liver II.	+
Kidney III.	+	Kidney III.	+	Kidney III.	0	Kidney III.	+
Liver III.	+	Liver III.	0	Liver III.	0	Liver III.	+

Number of cultures	24
Number of growths	18
Percentage	75.0
Number of organs	18
Number of bacteria-containing	14
Percentage	77.7

Set IV.

Series VII. (Cats fasting.)

Agar.	Broth.
Kidney I. +	Kidney I. +
Liver I. +	Liver I. +
Kidney II. +	Kidney II. 0
Liver II. +	Liver II. +
Kidney III. 0	Kidney III. 0
Liver III. +	Liver III. +

Series VIII. (Cats full fed.)

Agar.	Broth.
Kidney I. +	Kidney I. +
Liver I. +	Liver I. +
Kidney II. +	Kidney II. 0
Liver II. +	Liver II. +
Kidney III. +	Kidney III. +
Liver III. +	Liver III. +

Number of cultures	24
Number of growths	20
Percentage	83.3
Number of organs	18
Number of bacteria-containing	14
Percentage	77.7

Set V.

Series IX. (Dogs full fed.)

Agar.	Broth.
Kidney I. 0	Kidney I. +
Liver I. +	Liver I. +
Kidney II. +	Kidney II. +
Liver II. +	Liver II. +
Kidney III. +	Kidney III. +
Liver III. +	Liver III. +

Series X. (Dogs fasting.)

Agar.	Broth.
Kidney I. +	Kidney I. +
Liver I. +	Liver I. +
Kidney II. +	Kidney II. +
Liver II. +	Liver II. +
Kidney III. 0	Kidney III. +
Liver III. +	Liver III. 0

Number of cultures	24
Number of growths	21
Percentage	87.5
Number of organs cultivated	18
Number containing bacteria	16
Percentage	88.8

Set VI.

Series XI. (Rabbits full fed.)

Kidney I. Dry +	Kidney II. Dry 0	Kidney III. Dry +	Kidney IV. Broth +
Kidney I. Broth +	Kidney II. Broth 0	Kidney III. Broth +	Kidney IV. Agar +
Liver I. Broth +	Liver II. Dry 0	Liver III. Agar 0	Liver IV. Agar +
Liver I. Dry +	Liver II. Broth 0	Liver III. Dry 0	Liver IV. Broth +
Liver I. Agar +	Liver II. Agar 0	Liver III. Broth +	Liver IV. Agar +

Number of cultures	20
Number of growths	13
Percentage	65.0
Number of organs cultivated	12
Number of bacteria-containing	9
Percentage	75.0

SUMMARY.

Total number of animals	34
" number of organs cultivated	93
" number of cultures	122
" number of growths on cultures	95
Percentage	77.8
Number of organs containing bacteria	75
Percentage	80.6

AUTOPSY CULTURES. ROYAL VICTORIA HOSPITAL.

II., 1900. Male, 45. Plastic peritonitis with pneumothorax.

Eight hours after death.

Kidney,	Colon.	
Liver,	Colon.	
Spleen,	Staphylococcus.	

III., 1900. Female, 42. Chronic interstitial nephritis and uræmia.

Twenty-five hours after death.

Liver,	Colon.	
Spleen,	Colon and paracolon.	

VI., 1900. Male, 64. Chronic phthisis.

Sixteen hours after death.

Kidney,	Colon and staphylococcus.	Gas produced (Cultures).
Liver,	Colon.	Gas produced (Cultures).
Spleen,	Staphylococcus.	
	Paracolon.	No gas produced.
	Long putrefaction (2) forms.	(Cultures.)

VIII., 1900. Female, 10. Tuberculous meningitis and miliary tuberculosis.

Sixteen hours after death.

Kidney,	Staphylococcus.	
Liver,	Staphylococcus.	
Spleen,	Staphylococcus.	

IX., 1900. Male, 58. Mitral stenosis and incompetency.

Twenty-four hours after death.

Kidney,	Staphylococcus.	Gas produced.
	Colon.	
	Long thick bacilli.	
Liver,	Colon.	
	Long forms.	Gas produced.
	Broad forms.	
Spleen,	Colon.	Gas produced.

X., 1900. Female 30. Cholecystenterostomy. Death from exhaustion; no peritonitis.

Eight hours after death.

Kidney,	Staphylococci.	
	Mixture of bacilli which did not grow.	Gas produced.
	Colon.	

Liver,	Staphylococci. Mixture of bacilli. Colon.	Gas produced.
Spleen,	Staphylococci. Mixture of bacilli.	Gas produced.

XI., 1900. Female, 18. Cerebral abscess following otitis media.

Sixteen hours after death.

Kidney,	Staphylococcus. Mesentericus fuscus.	Gas produced.
Liver,	Staphylococcus. Mesentericus fuscus (vulgatus).	Gas produced.
Spleen,	Staphylococcus. Long narrow bacilli.	Gas produced.

XII., 1900. Female, 43. Alcoholic neuritis.

Six hours after death.

Kidney,	Staphylococcus Mesentericus fuscus.	No gas produced.
Liver,	Staphylococcus. Colon. Mesentericus fuscus.	Much gas produced.
Spleen,	Staphylococcus. Colon. Mesentericus vulgatus.	Much gas.

XIII., 1900 Female, 65. General peritonitis following stricture and ulceration of rectum.

Eight hours post-mortem.

Kidney,	Staphylococcus. Mixture of bacilli.	Gas produced.
Liver,	Mesentericus fuscus. Mixture of bacilli.	Gas produced.
Spleen,	Mesentericus fuscus.	Gas produced.

ANAËROBIC CULTURES. ROYAL VICTORIA HOSPITAL.

X., 1900. Eight hours after death.

Kidney,	Staphylococcus.
Liver,	Staphylococcus.
Spleen,	Paracolon.

XI., 1900. Sixteen hours after death.

Liver,	Colon.
Liver,	Staphylococcus. Long bacilli.
Spleen,	Staphylococcus. Long bacilli.

XII., 1900. Six hours after death.

Kidney,	Staphylococcus.
Liver,	Staphylococcus.
Spleen,	Colon.

XIII., 1900. Eight hours after death.

Kidney,	Paracolon. Mixture of bacilli. Long narrow bacilli without visible growth.
Spleen,	Staphylococcus.

AUTOPSY. ROYAL VICTORIA HOSPITAL.

II.—1900	Kidney +	XI.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
III.—1900	Kidney ?	XII.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
VI.—1900	Kidney +	XIII.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
		ANAËROBES.	
VIII.—1900	Kidney +	X.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
IX.—1900	Kidney +	XI.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
X.—1900	Kidney +	XII.—1900	Kidney +
	Liver +		Liver +
	Spleen +		Spleen +
		XIII.—1900	Kidney +
			Liver +
			Spleen +

Total: 26 organs cultivated, all contain bacteria.

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PHYSIOLOGICAL DILATATION AND THE MITRAL SPHINCTER AS FACTORS IN FUNCTIONAL AND ORGANIC DISTURBANCES OF THE HEART.

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In 1889 the reader[1] reported a series of observations of the hearts of men examined under nervous excitement. The conclusions arrived at were that under such conditions the mitral sphincter may be dilated by internal pressure, and the valve thereby may cease to be efficient, and regurgitation may occur into the auricle. It was further contended that as a pure physiological disarrangement the mitral valve may become functionally inefficient from causes that weaken the sphincter-like action of the circular fibres of the heart, and that this was the true explanation of many functional murmurs, so-called, as well as what is known as "relative mitral incompetency."

I now return to the subject. The muscular fibres of the walls of the heart are arranged in three layers. The external and internal layers run longitudinally, while those of the middle layer run around the heart as circular fibres, and are the principal propulsive power of the heart. A special layer of these circular fibres surround the left auriculo-ventricular opening as a sort of sphincter (Henle, Landois). For the sake of descriptive convenience these may be called the mitral sphincter, although they are only a part of the great cone of circular fibres which squeezes the blood out of the ventricle. A knowledge of this anatomical arrangement is important.

It should be understood that what is said here regarding the physiology of the mitral valve is true of the tricuspid, but for the sake of convenience I confine myself to the mitral.

1 Medical Record, April, 1889.

The mitral sphincter as a factor in the normal mechanism of closing the mitral valve is recognized by physiologists (among others, Tigerstedt, Curtis, Chauveau and Faivre, and Hesse), but not by all clinicians. A fairly thorough search of the standard American and English text-books on general medicine and diseases of the heart discloses the fact that with a few noteworthy exceptions medical writers do not seem to recognize this mechanism of the mitral valve, or, if they do, the important rôle played by it.

Whether the sphincter action is supplementary only to the closure of the valves or whether it is necessary for complete sealing of the opening under ordinary conditions is not clear; but that under extraordinary conditions a failure of this sphincter-like mechanism results in mitral and tricuspid incompetence is susceptible of experimental proof.

We have the following series of facts:

1. *Anatomico-physiological Facts.* The mitral orifice differs anatomically from the aortic orifice in not being, like the latter, circumscribed by a rigid ring of fibrous tissue, and, therefore, of fixed calibre. The fibrous tissue of the mitral ring, as Sibson showed by dissection, is so thin opposite the central attachment that practically the orifice is only partially surrounded by it, and hence the orifice dilates and contracts with the dilatation and contraction of the ventricles, this being effected by the sphincter. What holds the opening against the internal pressure is not a rigid ring, but the tonus and spasm of the circular band of fibres.

The researches, among others, of Chauveau and Faivre, and later of Hesse, have demonstrated that during systole the circumference of the base of the ventricle and of the auriculo-ventricular openings is contracted to a high degree. In other words, the auriculo-ventricular openings contract during systole and dilate during diastole. Hesse[1] actually succeeded in obtaining casts of the ventricular cavities in diastole and systole, and in obtaining hardened hearts in the same stages, and from these he made sections. Hesse's results are shown

[1] The method employed was the following: The ventricles of a dog's heart immediately after being excised were subjected to the pressure of a column of blood equivalent to 150 mm. Hg., and a plaster cast then taken. Then, the chambers being emptied, the heart was plunged into a saturated solution of bichromate of potash, whereby the muscles contracted without resistance. Thus two casts were obtained representing two conditions: the one representing the heart filled to nearly its full capacity, and the other extreme contraction

by these diagrams. The great difference in the dimensions of the auriculo-ventricular openings is noticeable, and it is also evident that with the expansion of the base during diastole these openings dilate, and with contraction of the base during systole they contract. As these findings are actual casts and sections of the ventricular cavities, it is difficult to see that they do not represent possible variations in the physiological size of the auriculo-ventricular openings. On the other hand, it is not safe to conclude that these findings represent the actual variation in normal diastole and systole during life, but only that they are the possible limits of physiological variations. It is true, they portray extreme conditions beyond what probably ever is observed in immediately successive periods of time in one and the same heart during life. But nevertheless they demonstrate, and this is the point, that the auriculo-ventricular opening has a varying calibre, that it is capable of being dilated to a large degree and of being contracted by the sphincter muscle to a comparatively small dimension, and that in systole it does contract.

It still remains an unsettled point whether, under *normal* conditions, the action of the mitral sphincter is only supplementary or whether it is necessary, but the following may be stated:

1. The elastic fibrous ring is variable in size under moderate pressure.

2. That without the sphincter action the internal pressure would force the valve, for there would be nothing to keep the orifice from dilating but this muscle, and, therefore, that the sphincter is essential for *maintaining* a sealed orifice, though perhaps not for the apposition of the valves under ordinary conditions.

3. Under ordinary conditions the tonus of the sphincter is sufficient to keep the orifice within such limits that the valves can close it (King, Chauveau and Faivre, Colin, Baumgarten and others), and, therefore, that merely filling the ventricles with fluid brings the valve curtains into apposition.

4. When for any reason the tonus of the sphincter is diminished or its muscular strength impaired, it may physiologically dilate to so high a degree in diastole that closure cannot take place without the aid of its contraction, and the sphincter may not be able to hold against internal pressure.

5. That under similar conditions the *degree* of contraction of the

muscular fibres may not be sufficient to enable the valves to hermetically seal the orifice.

6. It is probable, therefore, that under certain conditions the action of the sphincter is supplementary, and under other conditions it is necessary.

I. Experimental Conditions in which Physiological Dilatation and the Mitral Sphincter are Factors.

Very valuable information on the physiological working of the heart has been given us by the brilliant experimental researches of Roy and Adami,[1] which throw light on the part played by the auriculo-ventricular sphincter in health and disease. This work does not seem to have received the attention from clinicians that it has from physiologists or that which its practical importance demands. I shall, therefore, describe it here in some detail. These experimenters undertook to determine the physiological and pathological effect upon the heart of varying increase of work done. The method adopted to increase the work done was to increase the "pressure against which the heart has to force out its contents by narrowing the aorta at one or another part of that vessel."

The volume of the heart and the contraction of the muscular fibres were measured by special instruments and shown by graphic tracings.

A few of the more striking facts obtained are thus given:

"We may say that as the outflow of blood from the heart is interfered with the maximum pressure within the ventricle increases, this increase in pressure having a limit. . . .

"Such narrowing of the aorta produces a very evident distention of both ventricles, which, nevertheless, go on contracting and expanding in what to the eye seems a perfectly normal manner. Examination of the large veins, however, shows that in them, with the great or extreme narrowing just referred to, there is a very visible wave proceeding from the heart with each ventricular systole; in other words, this narrowing of the aorta produces regurgitation through both mitral and tricuspid valves. The effect, then, of greatly increasing the resistance which the ventricles have to overcome in the evacuation of their contents, is to raise the intraventricular pressure during systole to a height varying with the individual heart under observa-

[1] Remarks on Failure of the Heart from Overstrain, by Prof. Roy and J. G. Adami, British Medical Journal, December 15, 1888.

tion, and to cause great expansion of the chambers of the heart with regurgitation eventually through the auriculo-ventricular valves.

"The heart itself, however, is appreciably affected by such change in the blood-pressure. Its size at the end of systole is greater than with normal arterial pressure—that is, there is not so complete an expulsion of blood; while, at the same time, its expansion during diastole is also greater. . . . The result is, that when the arterial pressure rises the volume of blood in the heart, both at the end of systole and at the end of diastole, is increased. Analogous results are produced when the arterial pressure is raised by other methods. In other words, the effect of variations in the arterial pressure on the heart is that increased resistance produces diminution of the systolic contraction of the ventricles, and the quantity of the blood entering the heart in any given time remaining the same, this diminished contraction is, *cæteris paribus*, necessarily accompanied by increased expansion in diastole.

"We have seen that in the experiments first referred to the expansion of the heart so produced leads, if extreme, to functional incompetence of the auriculo ventricular valves, an effect which is all the more readily produced the more fatigued the heart is.

"There is also the fact that increase in the work done, other things being equal, produces diminished completeness of contraction in systole, and, therefore, an increase in the residual blood in the ventricle. This *physiological dilatation* of the heart with increased work becomes, when excessive, the cause of failure of the organ from overwork, or overstrain, as it is generally called; in other words, in such cases the heart goes on contracting and sending out all the blood which reaches it (excepting, of course, the residual blood) until the moment when, either from increase in the arterial pressure, or from weakness of the heart-muscle resulting from fatigue or from disease of its walls, *the muscles at the basis of the ventricles no longer in systole narrow the auriculo-ventricular orifices to a degree which permits of these orifices being closed by their valves, these not being capable of expanding to the same extent as the muscular substance of the heart.*"

It will be observed that Roy and Adami interpret the regurgitation as due to physiological dilatation of the sphincter alone. But from their experiments it is not clear that the closure of the valves may not also be hindered by the dilatation of the ventricular wall, which, carrying the papillary muscles with it, pulls apart the valves. Probably both factors co-operate. Prof. William T. Porter informs me that he has observed in dogs this physiological dilatation of the heart working against increased arterial pressure from contraction of the aorta.

Roy and Adami made a further very extended series of observations upon the effect upon the heart of both direct and reflex excitation of the vagus and augmentor nerves. The excitation of the vagus,

they find, among other things, to produce substantially the same effect as when the arterial resistance is increased, namely, a physiological dilatation.

The consequence of this dilatation is that the amount of blood expelled at each beat may be doubled, trebled, or even quadrupled. The increase of the residual blood may be so great that, as can be seen from the cardiometric tracings, *the volume of the heart at the end of systole may be greater than was the volume of the organ at the end of diastole before the vagus nerves had been excited*. Nevertheless—and this seems to me to be a point of some significance in its bearing upon the capacity of the sphincter muscle to completely close the mitral valve in conditions of dilatation—nevertheless, the ventricular contractions are less completely made; *there is less complete systolic shortening of the ventricular fibres*, due to the more distended condition of the ventricles and the increased contraction-volume. This being the case, the systolic constriction of the auriculo-ventricular orifices must also be less complete. The effect is the same, whether the vagus be directly stimulated or indirectly by reflex action, excepting that in the latter case an important element may be added, namely, a rise in the arterial pressure which still more tends to dilate the heart. Stimulation of the vagus may further cause physiological irregularity of the heart, as a necessary consequence of the arrangement by which the vagus governs the heart.

An opposite effect is observed when the *nervi augmentores* are excited *directly and alone*, for then, besides an acceleration of the heart beat, the force of the ventricular contractions is increased so that the ventricles contract more completely and diminish the amount of residual blood, in spite of the fact that the arterial pressure is raised at the same time.

But when the augmentors, alone or together with the vagi, are *indirectly* excited by stimulation of a sensory nerve, the effect upon the expansion of the heart often resembles that seen in excitation of the vagus, for the rise in arterial pressure is not always completely counterbalanced by the increase in the force of the heart's contraction, and the heart becomes expanded in diastole and systole. In other words, the result is physiological dilatation. It is obvious that this reflex excitation more nearly approximates the physiological excitation which occurs in the organ, however great the divergence may be,

and though these experimental effects may not exactly express what does normally occur, they demonstrate the possibilities.

As Roy and Adami point out:

"The importance of this want of accordance between the increase in the force of the left ventricle and the increase in the work which it is called upon to do, can hardly, we think, be overestimated, and in a future section we will make such comments upon it as appear to us of practical interest to the physiologist and the physician; in the meantime we need only say that the physiological dilatation of the left ventricle, which often enough shows itself in spite of augmentor action is, in the hearts of healthy, well-fed animals, moderate in amount, and does not lead to any diminution of the output of the organ. In the case, however, of animals with weak hearts, this physiological dilation may assume excessive proportions, and may lead to failure of the auriculo-ventricular valves and diminution of the output of the heart; in other words, to heart failure from inability to meet an increase of work which a healthy, well-fed heart can bear without difficulty."

One of the most valuable results of the work of Roy and Adami has been to show that the heart within pure physiological limits is not an organ of definite size, but contracts and expands in accordance with an automatic mechanism by which it adapts itself to the work to be done, and during expansion the circular fibres shorten less than when of smaller dimension. It is a pump, but a pump that changes its size from time to time.

There, is then, such a thing as physiological dilatation and physiological incompetence. They represent the adaptation of the organ to the work to be done. Pathological dilatation differs from the physiological variety only in degree, and is a result of the same law, viz., a disproportion between the work to be done and the power to do it. One may shade into the other when the forces that produce physiological dilatation become excessive. It is then quite possible that from purely physiological variations of the working of the heart we may have disturbances of its functions which are essentially the same in character as those met with in pathological conditions, namely, valvular incompetence, irregularity, and other variations of rhythm.

II. Clinical Conditions of Health in which Physiological Dilatation and the Mitral Sphincter are Factors.

While Roy and Adami were pursuing their experimental studies the reader was engaged in a series of observations on the clinical side,

but which in some respects took on the character of an experimental study, namely, the action of the heart under intense nervous stimulation, as shown by the occurrence of murmurs.[1] For some years previously I had noticed, in examining the applicants for the Boston Fire Department, a very unusual, and to me then, unaccountable frequency of heart murmurs. The conditions of the examination were such that a large proportion of the men were under strong emotional excitement. This was shown by the frequent occurrence of violent heart action, general nervousness, and tremor of limbs and voice. A systematic study was finally undertaken; the heart was intentionally artificially stimulated as much as possible by the method of examination. The applicant was ushered into the room without warning of what was to occur; he was urged to be quick in his movements and prepare himself as rapidly as possible, and the heart was examined as the first event. The ordeal was made as exciting as possible, and, as a matter of fact, the heart in a large proportion of cases was found to be working under intense stimulation and doing—if the force of the heart's beat on the chest-wall and the loudness of the sounds be criteria—an increased amount of work. It is important to bear this in mind in studying the results.

The total number of cases in the first series examined was eighty-six. Of these nine were thrown out on the ground of disability from organic disease, there being evidence of an enlargement in six, and in one of irregularity. The rejection of seven of these I now think was a mistake. However, in the seventy-seven remaining, mitral systolic murmurs were heard in twenty-five. So-called exocardiac or cardio-pulmonary murmurs were taken into account, examined for and excluded. Still, I feel sure that in some instances these were confused with endocardiac murmurs, and the total frequency of murmurs thereby increased. In a second series of eighty-five cases exocardiac murmurs alone were heard ten times, while in fourteen cases true endocardiac murmurs were heard.

To determine the relation of these murmurs to nervous excitation, in the first fifty-six subjects the heart was examined under the same conditions as in the first series; in the last twenty-nine the heart was examined last, after reasonable time had been given to the applicant

[1] The Occurrence and Mechanism of Physiological Heart Murmurs (endocardial) in Healthy Individuals. Medical Record, April 20, 1889.

to become accustomed to the ordeal. The result was that in the first fifty-six subjects the mitral systolic murmur was heard eleven times, and an exocardiac (cardio-pulmonary) murmur nine (or more) times. In the last twenty-nine subjects a true mitral murmur was heard only three times and an exocardiac murmur once.

In a third series (not hitherto published) out of a total of 103 individuals, and omitting two cases in which there *might* have been organic disease, systolic murmurs at the apex were heard in 21.

As corroborative evidence of the occurrence of these murmurs *under these conditions*, I asked Dr. J. H. McCollom to note the number he found independently in his examination of applicants for the Police Department. He stated that in a first series he found 27 mitral murmurs in 200 men, and in a second series of 111 men, 18 such murmurs.

In a *fourth series* of my own the conditions of the examination were altered so as to eliminate all emotional excitement. The result was that only a so-called pulmonic systolic murmur was heard three times, once being accompanied by a "mitral systolic of a temporary character," but heard after forced expiration. Further hundreds of cases have been examined in the same way since this time. Only occasionally in a nervous individual will a functional murmur be heard, perhaps in 1 or 2 per cent. of the cases.

I have given the statistical results of these observations, but I do not wish to lay any great emphasis upon the figures from the point of view of *interpretation* of the sounds heard. Only one who is in the habit of making examinations of this kind can realize the difficulty of always correctly distinguishing between an exocardiac or cardio-pulmonary murmur and a true mitral murmur. They sometimes simulate each other in an extraordinary way. In some cases the short time given to interpret the character of a murmur, owing to its rapid evanescence with the allayment of nervous excitement, makes it extremely difficult to correctly classify it. This and the fact that many exocardiac murmurs in their physical peculiarities closely resemble true mitral murmurs, in spite of all rules regarding their differences, make it certain in my mind that some of these murmurs, though tabulated as endocardiac, were really exo-cardiac. For instance, it was only lately that I had the opportunity to listen to an extremely loud systolic murmur at the apex. It was

heard still louder in the axilla, and was plainly heard in the back. For this reason for the moment I thought it was mitral, but I was soon able to make out that the pitch and quality were pulmonary, and it was heard to the left rather than over the apex. There was another murmur of different quality to be heard at the apex, but this was probably transmitted from the base, where there was a so-called "pulmonic" systolic murmur. Both subsided after a few minutes. The first murmur I believe to have been cardio-pulmonary.

I do not, therefore, lay any stress upon the statistical frequency of this mitral murmur. The figures I have given are, I have no doubt, too high. The important fact is that, without reference to frequency, a greater or less number of murmurs indicative of mitral regurgitation do occur under the conditions of observations, viz., extraordinary nervous excitation of the heart. As I have already described[1] at some length the character of these regurgitant murmurs, and given the reason for this interpretation, a brief statement on this point must suffice.

1. Their physical characteristics, including location, point of maximum intensity and transmission fulfilled all the requirements of a mitral murmur.

2. The only murmur for which they could be mistaken is the cardio-pulmonary, and in doubtful cases, not uncommonly two distinct systolic apex murmurs could be heard, one distinctly cardio-pulmonary; the other evidently must have been regurgitant.

3. They were persistent after forced expiration.

4. In a large number of cases, a systolic murmur of similar character was plainly audible in the second left intercostal space, either close to or about one and a half inch from the sternum, the so-called pulmonic murmur, which is regarded by many observers (Balfour, Naunyn and others) as due to mitral regurgitation.

5. They are sometimes heard at the junction of the fourth rib and sternum on the left (*i. e.*, over the mitral valve).

6. The pulmonic second sound, as might be expected, is rarely relatively or absolutely accentuated, owing undoubtedly to a synchronous rise of arterial tension and because of the small amount of mitral leakage.

In my first communication the explanation which was given of

[1] Medical Record, April, 1888.

these mitral murmurs was that *under strong nervous excitement the powerful contraction of the circular fibres of the heart so increased the pressure within the cavity of the ventricle*[1] *that the mitral sphincter is forced, so to speak—that is, it is either dilated or prevented from contracting sufficiently for a complete closure of the auriculo-ventricular orifice. Thus a functional regurgitation occurs.*

This mechanism I still believe to be an important factor in the case, but in the light of Roy and Adami's experiments the question of a possible accompanying and co-operative physiological dilatation of the heart assumed importance. It, therefore, became imperative that these observations should be repeated for the purpose of making accurate measurements of the size of the heart.

At the time of my first series of observations (1888) it never occurred to me, nor was it generally known, I think, that the healthy heart might dilate under conditions of increased effort (aside, of course, from quasi-pathological fatigue following excessive muscular exertion), so that when evidence of enlargement occurred the case was thrown out as possibly organic. Six cases, as before mentioned, were rejected for this reason. This, in view of later evidence, I believe to have been an error, and I am convinced that these cases were merely examples of functional dilatation. For in the first place, nine cases out of eighty-six men is far too high a proportion for heart disease to exist in presumably healthy men in the prime of life; and, second, I do not find anything like that proportion of existing organic disease under the present conditions of examination.

The third series of observations was, therefore, made for this purpose. Slight enlargement is not easy to demonstrate. Percussion is a very inexact method when precision is required, as has been shown by F. H. Williams' observations with the radiograph.[2] Percussion dulness cannot always be relied upon to correspond exactly with the outline of the heart. The position of the apex (as well as the apex-beat) of the heart is sometimes more exact, but it also has its fallacy aside from tilting.

Nevertheless, in this series I was able to satisfy himself of the presence of fugitive enlargement to the left in quite a number of cases.

[1] The same thing may be true of the right ventricle.
[2] Philadelphia Medical Journal, January 6, 1900.

In them the line of dulness along the left border of the heart extended through the nipple, and the apex-beat could be seen or felt in this same line, and even well outside of it. Sometimes at the end of the examination it could be seen that the apex had receded to its normal territory and the line of dulness had also receded—that is, as the excitement subsided the heart retracted. Thus in about 10 per cent. of all cases an enlargement to the left was present, sometimes

FIG. 1.

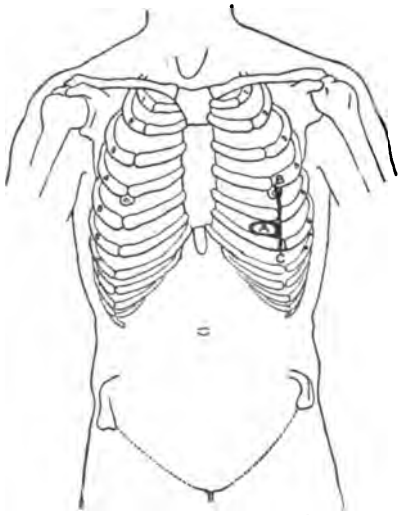


FIG. 2.

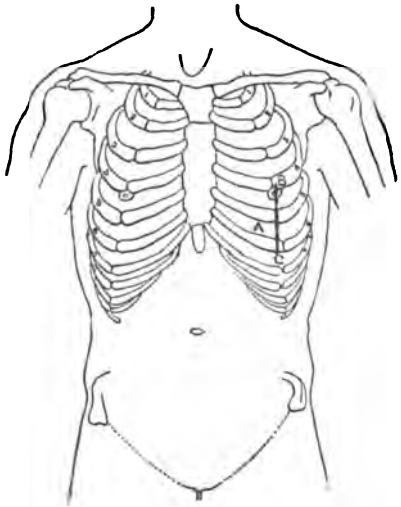
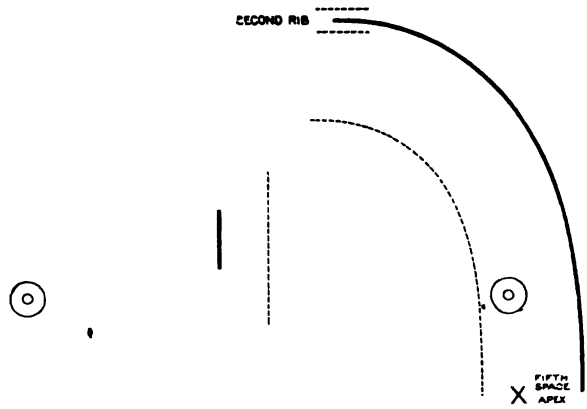


FIG. 1.—No. 42 (August, 1889). The apex-beat (A) was violent and occupied a larger area than usual. In this and Fig. 2 the line of dulness along left border only of heart is shown.
FIG. 2.—No. 85 (same date). Loud and low-pitched mitral systolic murmur.

without murmurs. (See Figs. 1, 2, and 3.) Fig. 3 is particularly interesting. It is a late observation, and was made by first outlining the heart on the chest-wall by percussion, and then transferring by tracing-paper. The continuous line is that of cardiac dulness at the time of nervous excitement; the broken line the same after the heart had become quiet. The difference in the size of the heart is quite remarkable. The enlargement is to the right as well as to the left and above. The extension of dulness upward is interesting in connection with the experiments and observations of Foxwell, who has shown that this feature is characteristic of the condition of the heart in which the so-called pulmonic systolic murmur is heard. He

offers experimental evidence to show that it is due to the dilatation of the conus arteriosus, and the murmur to a distortion of the pulmonary artery, the dilatation itself being the consequence of debility. In the case from which this diagram was made at the time of the enlargement and excitement the heart's action was irregular, and a systolic murmur was present in the second space, heard loudest over the left auricle—that is, about one and a half inch from the sternum.

FIG. 3.



From tracings. Heavy line = cardiac area (dulness) during excitement; enlargement to right as well as to left and upward; broken line = same after subsidence of excitement same day and also six days later. × = apex-beat. During period of excitement, May 19, 1900, heart's action irregular, "pulmonic systolic" murmur (in left auricular area), loud cardio-pulmonary murmur to left of apex; after cessation of excitement disappearance of murmurs, and heart normal in every way. May 25th, heart still normal.

It was this case in which the very loud (presumably) cardio-pulmonary murmur (p. 424) was heard. During the course of the examination the heart became quiet and retracted in size and then the murmurs disappeared. Six days later, when examined again, the heart was still in every way normal.

I have thus been able to convince myself that in a certain proportion of cases the presence of dilatation is of a temporary nature. The following may be cited as examples:

No. 7 (already mentioned). At first, while the murmur was present, the apex-beat could be detected outside the mammillary line. Later, at the end of the examination, the apex receded inside the mammillary line, but close to it.

No. 12. Mitral systolic; a strong apex-beat outside the mammillary line;

heart action rapid and violent. A loud systolic murmur could be heard over the aortic orifice; also over the pulmonic. It may have been this murmur that was continued to the apex. Subject very nervous, voice tremulous. Later, murmurs disappeared, heart became quiet, and the apex-beat scarcely visible, and retracted close to but within the mammillary line.

No. 14. Heart-sounds normal; apex-beat in the mammillary line; heart's action violent. Later, the apex-beat receded inside the mammillary line.

No. 31. A rough mitral systolic murmur at the apex; apex-beat in the sixth space at the inner edge of the mammillary line.

No. 37. Mitral systolic murmur; percussion dulness extended on the left through the mammillary line. When examined some days later all these murmurs had disappeared and the line of dulness had retreated to within normal limits.

No. 42. At the beginning of examination, mitral systolic murmur, which later disappeared. Heart's action rapid and supernormal in strength; apex-beat could be both seen and felt close up to the mammillary line, extending over a wider area than normal. The line of the percussion dulness extended also through the mammillary line.

No. 58. First sound at the apex normal, but a systolic murmur could be heard over the aortic opening and continued in the carotid. The apex-beat could be felt with the finger in the mammillary line and percussion gave the left border of the heart as extending through this line. When examined a few days later all these murmurs had disappeared and the line of dulness had retreated to within normal limits.

In some instances, as would be expected, there were evidences of enlargement of the heart without any signs of incompetency of the valves; for example, Nos. 14, 34, and 36. In a great many instances when I have examined these subjects some days later under circumstances that allayed all apprehension, the murmur previously heard had entirely disappeared, as well as all signs of cardiac dilatation. To these cases I would also add the six instances in the first series of observations, which were eliminated because of the enlargement of which I had found evidences, and because of which I had concluded that they were probably of organic origin.

In the light of these findings, then, I think we may conclude that under intense nervous stimulation of the heart, *presumably tending to increase the work done*, there may occur a physiological dilatation of the heart similar to that which occurs when the pressure is raised by the methods employed in the physiological experimentation already referred to, and that the mitral sphincter also shares in this physiological dilatation. This means that its contraction, that is, the shortening of

the circular fibres, is less complete, and the orifice is larger at the end of systole than normal. In consequence of this and of the increase of internal pressure, the contraction of the sphincter may be impeded, or even expanded, by the hydrostatic pressure, and the valve may become incompetent and regurgitation may take place.

I have omitted various details of these observations for the sake of brevity. It ought to be noted, however, in evidence of the intense stimulation of the heart that was usually present, that murmurs were frequently heard over other regions of the heart than at the apex. (Sir W. Broadbent has lately pointed out the frequency of murmurs over the various orifices of the heart in subjects undergoing civil service examinations, and to this extent has corroborated the accuracy of these observations. He warns against the danger of mistaking them for evidences of organic disease.) The heart's action was usually increased in rapidity, sometimes to a very high degree, and its action was often violent and tumultuous. The apex-beat was sometimes diffused over an area of about double the extent of that which is normal. It was quite common to have all these signs disappear during the course of the examination, even while one was listening, and to see the increased cardiac area retract within normal dimensions.

In line with these observations of my own are those of Dr. John C. Munro,[1] who made an investigation into the condition of the heart in fifty-seven patients before and after surgical operations. The conditions before operation were considered to be those of apprehension and nervousness. Of the fifty-seven cases there was a group of fourteen in whom there were evidences of cardiac disturbance before operation, all signs of which disappeared as soon as the operation was over. In thirteen of these cases there was a systolic murmur at the apex; in the other one, a presystolic murmur. Besides these there were six other cases which exhibited functional disturbances which persisted after the operation, while eight, it was thought, had well-marked organic disease, a very high and suspicious percentage. These findings of Dr. Munro seem to be corroborative of the observations which I have just recorded.

In 1890 Theodor Schott demonstrated by examining the hearts of strong, healthy men, before and after wrestling, that strenuous

[1] Boston City Hospital Reports, Series VIII., 1897.

exercise, when intense, though of short duration, brings about a temporary dilatation of both sides of the heart. After a few minutes' severe wrestling, continued to a point to produce dyspnœa, an enlargement, shown by percussion, was produced both to the right and to the left from one to two centimetres and more. This dilatation duly subsided after a short rest; it does not appear, however, from Schott's observations, that the mitral sphincter was physiologically incapacitated by this dilatation, for he failed to find any regurgitant murmur, nor is any mention made of pulmonic murmurs, a rather striking contrast with the findings of others after long-continued and violent exercise sufficient to produce exhaustion. Schott interpreted this dilatation as the expression of an overstrain of the heart, and so stigmatized it with a pathological soubriquet. Overstrain is a clinical term, and is not descriptive of the physiological or pathological process. It may mean much or nothing. From the fact that there was no evidence of regurgitation it must be presumed that the contraction of the auriculo-ventricular sphincters were still sufficiently extensive to close the orifices. From this, and also from the fact that the wrestling was only continued three or four minutes, we are compelled to conclude that neither the internal pressure was sufficient to force the sphincters, nor was there true fatigue or excessive dilatation. A more correct interpretation would seem to be that the dilatation observed was simply physiological and identical with that observed in animals when the heart is called upon to do any great increase of work.

There is an economy in this physiological dilatation. According to mathematical laws, when the heart is dilated—that is, when the circumference is increased—a smaller amount of contraction will suffice to throw out a larger volume of blood. For instance, if the heart were a sphere of ten inches in circumference a contraction of the circumference of one inch would throw out 4.5 cubic inches of blood, while if it were only five inches in circumference the contraction would throw out only a little over one cubic inch,[1] and this is what occurs in physiological dilatation. A greater amount of blood is thrown out at each systole with diminished contraction. With a dilatation of moderate amount the degree of contraction is sufficient

[1] Roy and Adami.

to close the auriculo-ventricular orifices. But if the dilatation is excessive, either from great increase in the work to be done or weakening of the cardiac muscles, the contraction may not be sufficient in extent to close the orifice. As a rule, even with considerable dilatation, so long as the muscle is not fatigued the contractions of the sphincter are sufficient; but when fatigue sets in the contractions become shorter, the dilatation greater, and incompetency results.

It is interesting in this connection to notice that Schott found that by constricting the abdomen with a belt, and thus increasing the amount of blood flowing into the right ventricle, and thereby the amount of work to be done by the heart, the dilatation was thus further increased. This is in entire corroboration of the experimental observations on animals (Roy and Adami, Fry and Krehl), which have shown that compression of the abdominal veins causes dilatation of the heart by increasing the total output—that is, the work done. (Therein is a practical suggestion as to the possible ill effects of tight lacing.)

Later, in 1897, in another and similar series of experiments, Schott confirms these earlier observations by means of the skiagraph. The X-ray showed that the enlargement of the heart from side to side after strenuous exercise (wrestling) might be as much as 3 or 3½ cm. He also demonstrated the same thing after severe walking or bicycling. Undoubtedly fatigue of the cardiac muscle enters as an element in this cardiac dilatation when the enlargement follows persistent and severe exercise, and itself is persistent. Very interesting in this connection is the series of clinical cases which Schott gives of persistent dilatation of the heart following extended muscular exertion. This enlargement took on a pathological character, and more correctly may be regarded as the expression of overstrain of the heart or muscular fatigue. This dilatation followed various forms of muscular exertion, including bicycling, manual labor, and dancing combined with tight lacing. The symptoms were disabling and those usually observed in cardiac incapacity.

III. Quasi-pathological Conditions, in which Physiological Dilatation and the Mitral Sphincter are Factors.

In Schott's experiments there was no mitral incompetency, or at least this was not revealed by auscultation. It was otherwise with

the observations of Williams and Arnold of the hearts of the contestants in a Marathon running race of twenty-five miles. These are amongst the most valuable thus far recorded to determine the effect of fatigue upon the *human* heart. Of the ten men examined both before and after the race, seven showed, after running, a relative increase of the cardiac dulness extending to the left. It is interesting to note that the line of dulness corresponding to the left border of the heart, as shown by the published diagram, extended through the nipple and agreed very closely with the same line which I found in my own observations, where there was increase of the cardiac area, and with some of Schott's cases. In eleven out of thirteen men, murmurs were noted. In all cases these were systolic, and the authors, after an extended discussion, interpret them as of mitral origin. In explanation of this the authors adopt the view that fatigue induced a dilatation of the walls of the heart, including the mitral sphincter. In consequence of this physiological dilatation the auriculo-ventricular valves closed imperfectly, and regurgitation was allowed to take place.

Curiously enough, almost on the same day that Williams and Arnold presented the results of their observations to the Climatological Association, Stengel reported to this Association a similar series of observations of the hearts of athletes before and after running. He also found enlargement, and in some cases this enlargement was accompanied by mitral regurgitation. Stengel remarks that he has noticed the ease with which a systolic murmur developed over the hearts of men in the early part of their training for the football field when they are presumably out of condition. In a special trial of nine of the candidates he found that three promptly developed a very distinct murmur of this kind after a little exertion.[1]

[Since this paper was presented the writer had an opportunity to take part in the examination of the Marathon runners this year. For certain reasons the examination of the hearts was not entirely satisfactory. Murmurs were not heard, owing, probably, to tardiness in the examination, but enlargement was plainly demonstrable in most cases.]

The interest of these phenomena lies in the fact that they represent a general law. The dilatation and incompetency must be held to be the physiological result of increased work done, with diminished power to do it. Under the primary increased stimulation the

[1] Transactions of the Association of American Physicians, 1899. vol. xiv.

heart expands and throws out a greater volume of blood; then the organ becoming fatigued the power is diminished, and thereby the work is relatively still further increased, dilatation increases, and incompetency finally follows.

These observations of Stengel, Williams, Arnold and my own seem to me to be a complete physiological confirmation on the human subject of the experimental work of Roy and Adami on the dog's heart.

IV. Pathological Systemic Conditions in which Physiological Dilatation and the Mitral Sphincter are Factors in Determining Cardiac Disturbances.

As is well known, there are quite a number of conditions in which temporary mitral systolic murmurs are heard, often with enlargement. The most common conditions which these murmurs accompany are anæmia, Bright's disease, gout, arterial sclerosis, chorea, the infectious fevers, like diphtheria and typhoid, and even rheumatism. In some of these conditions there is presumably a weakened heart muscle—*e. g.*, infectious diseases and anæmia and other adynamic states. In others there is an increase of the arterial tension (Bright's disease, gout); in all cases enlargement is not infrequently present. Now, what I wish to point out is this: That the physiological principles underlying these cardiac disturbances is the same as in the experimental and other conditions which I have already discussed, and that the disturbances of function more nearly approximate physiological than pathological variations.

In my original paper I put forward the theory, as did also at the same time Roy and Adami, that the mitral systolic murmurs in these conditions represented physiological regurgitation due to incomplete contraction of the mitral sphincter, but to Donald MacAlister is due the credit of priority for this explanation, the first suggestion coming to him from Hesse's casts. As Roy and Adami put it: "When from any cause the muscular power of the heart is diminished, whether from imperfect blood-supply, fatty degeneration, or impaired quality of the blood, or from any of the known causes by which the power of contraction of the heart is impaired, we have a condition in which the relation between the work required of the organ and its power of doing that work is affected in an analogous way to that which occurs when the work of the heart is increased

and its power remains constant."[1] In Bright's disease and gout we have an increase of the work to be done while the power remains unchanged; in the febrile diseases the work remains the same, but the power is diminished.

As all experienced practitioners are familiar with the murmurs occurring in adynamic states it is not necessary to describe them at any length. In the course of Bright's disease it is not uncommon to observe evidences of temporary regurgitation from the left ventricle. I may cite here, for illustration only of what I mean, the case of a patient who was in the advanced stages of chronic Bright's disease, and also suffered from attacks of gout of a severe nature. The heart was very much enlarged, but no evidence of mitral incompetence, as a rule, could be detected. There were evidences of very high arterial tension. Every now and then he suffered from attacks in which a very loud mitral systolic murmur was heard at the apex. At such times marked œdema and congestion of the lungs were noticeable. Later these signs of mitral failure would disappear. Such attacks are usually called acute pathological dilatation or heart-failure. The proper interpretation of cases of this kind unquestionably is that under the extremely high tension present there occurs a *physiological*, not pathological, dilatation of the mitral sphincter with diminished contractions, preventing complete closure of the valve. The work to be done becomes augmented, the heart physiologically dilates, but, not being strong enough to meet the strain, dilates too much and allows incompetence. With the disappearance of the high tension the muscle contracts again and the incompetence disappears.

Diphtheria offers a particularly favorable opportunity to study cardiac insufficiency due to weakness of the muscle, for it is known that the toxin affects both the pneumogastric nerve (and presumably the augmenter nerves) and the muscle substance. It is, then, a good type of that class of affections in which the auriculo-ventricular sphincters are weakened, and as such I speak of it. First-rate data for such a study are furnished by the reports and observations of the many hundred cases in the Boston City Hospital, made by McCollom[2]

[1] "Failure of the Heart from Overstrain." In other words, the mechanico-physiological effect is the same, whether the power remains constant and the work is increased, or the work remains constant and the power is diminished.

[2] A Clinical Study of Eight Hundred Cases of Diphtheria at the South Department of the Boston City Hospital. Boston City Hospital Reports, 1898, Ninth Series.

and Hibbard.[1] From a study of two series of cases (one, 800, and the other 252 in number) Hibbard found that "a systolic murmur at the apex with an accentuated pulmonic second sound, and often with some enlargement of the cardiac dulness is seen in about 10 per cent. of the diphtheria cases during the course of the disease." This murmur is temporary, for in twenty-four cases kept continuously under observation, it disappeared within three weeks in twenty-one cases and within eight weeks in the remaining three. The enlargement was found to extend in some cases in children as much as two centimetres outside the normal limit. Out of 121 fatal cases McCollom noted a mitral systolic murmur in eighteen cases, or nearly 15 per cent., and of these eighteen an enlargement was detected in six. In only one was there an enlargement without a murmur. An analysis of the cases which were fatal, chiefly from heart complications, and in which an autopsy was held(twelve in number), is instructive. Of these twelve a mitral systolic murmur was heard in seven. The auriculo-ventricular valves were found dilated *after death* in three, one or both ventricles dilated in five, and the heart enlarged by weight in eleven.[2] It must not be forgotten that the absence of dilatation either of the openings or the cavities after death is not evidence that it did not exist during life, as it is well known that after death the cardiac muscle contracts strongly (King, Sibson, and others).

A sufficient cause for the muscular weakness is found in the known action of the diphtheritic poison on the nerves of the myocardium. Thus of five cases of mitral insufficiency the pneumogastric nerve was found diseased in all.[3] It is an instructive fact, and one demonstrating that marked dilatation is not essential for physiological regurgitation, that out of the eighteen mitral systolic murmurs McCollom reports that no enlargement of the cardiac area could be detected in twelve. This properly interpreted means *that the mitral sphincter may not sufficiently contract, even though the dilatation is not sufficient to be detected by the usual methods of physical diagnosis.*

In view of the post-mortem findings, the mitral murmurs in this class of cases unquestionably represent regurgitation. In those cases

[1] Heart Complication in Diphtheria. Ibid.

[2] The cause of increased weight was not determined.

[3] In every case (9) where the nerve was examined it was diseased. In some the myocardium also was degenerated.

where regurgitation occurs without the coexistence of dilatation the only intelligible conception of the conditions present is that the mitral sphincter is so weakened by disease that it does not sufficiently contract against even a normal or subnormal arterial tension.

In other cases when there is dilatation there does not seem to be any reason to suppose that the etiological principle is not physiological rather than pathological, or that it differs in any way from that which has been experimentally demonstrated to obtain in healthy animals. The work to be done by the heart is relatively increased—that is to say, the work remains the same, but the power is diminished; hence, the heart is called upon for increased effort, and physiological dilatation results. This dilatation again increases the difficulty of the auriculo-ventricular sphincter.[1] Thus it is that the muscular inefficiency of the heart calls into play the physiological law of increased work. In other systemic conditions, like arterio-sclerosis, as I have said, there is no weakness of the cardiac sphincter, but an excessive increase of the work to be done (increased arterial tension).

V. Pathological Conditions of the Heart in which Physiological Dilatation and the Mitral Sphincters are Factors in Determining Disturbances of the Organ.

Space will not allow me to more than allude to some of the perturbations which complicate the phenomena of cardiac disease and which are occasioned by these physiological factors.

If these factors, dilatation and sphincter action, are physiological laws, they must be universal in their action, and affect diseased as well as normal hearts. And hence it well may be that, looked at from this point of view, some of the commonly observed manifestations of heart disease may really be physiological in principle, exaggerated perhaps by the fact of the organ being incapacitated.

From the point of view of practical therapeutics this distinction at once becomes important. The conditions of "overstrain" of the heart, with relatively persistent dilatation and mitral incompetency,

[1] In extreme cases, when the dilatation is excessive, the mitral incompetency may be caused or increased by the bulging of the walls, which, carrying away the chordæ tendinæ, prevents the valve flaps from coming into apposition. In most cases the dilatation is too slight for this.

"fatigued heart," "curable mitral regurgitation" and acute dilatation, I need not more than allude to, as they have already been discussed (Section II). They are substantially one and the same condition, originating in and growing out of physiological dilatation from increased work. It may be that the difference between the physiological and the pathological is only one of degree. The tremendous strain sometimes put upon the heart induces necessarily a dilatation. To this "fatigue," as yet an incompletely known condition, becomes added and the dilatation becomes persistent.

The mitral sphincter necessarily shares in the inefficiency. When we bear in mind that by simply increasing the work the volume of the healthy heart may be so increased that its size at the end of systole may be even greater than it was before at the end of diastole, and that the volume of blood thrown out may be quadrupled, we can appreciate the dilatation that may be affected by the enormous exertion to which the heart is sometimes subjected and yet be physiological. Add to this "fatigue" and loss of muscular tone, and the effect of the law is apparent. It was only lately that I was called to pass upon the condition of a man who had undergone great muscular exertion and had fallen down unconscious. On recovery he had developed persistent symptoms of cardiac disease, with dilatation (dizziness, pain, palpitation, cyanosis on exertion, etc.). He had been examined by several competent physicians, all of whom, I am told by the attending physician, diagnosed the case as "myocarditis." The subsequent history bears out the opinion that it was one simply of physiological dilatation and overstrain.

In fatty degeneration and other degenerative diseases of the heart the weakening of the myocardium tends to weaken the sphincter and make the heart dilatable under very slight exertion.

In valvular disease, especially in aortic stenosis, the increased work which the heart is called upon to perform tends to increase the normal dilatations which occur from time to time and to make less complete the action of the sphincters. In this way it seems to me are to be explained many of the acute dilatations and temporary mitral regurgitations which occur in the course of aortic disease. The increase of power coming from hypertrophy has the tendency to keep the dilatation within physiological limits, but sooner or later this compensation becomes inefficient.

The further application of these principles is readily made, and need not be further discussed.

All the observations to which I have referred in Sections I. and II. are particularly instructive as pointing to the very large variation that may take place in the size of the heart of the human being under actual conditions of life, and be within physiological limits. They render comprehensible that within physiological limits the mitral valve may fail to do its share in the closure of the mitral orifice. They contribute to what might be regarded as the modern conception of the heart's workings and of a certain class of cases of mitral insufficiency which formerly were regarded as purely pathological, but now are recognized to be due to muscular weakness, and curable. The experiments on animals enable us to understand the *modus operandi* of the Nauheim treatment, for it has been experimentally shown that excitation of the peripheral nerves may reflexly stimulate the augmenter nerves of the heart, and through them increase the force of the contractions and the completeness of the systole, and diminish the quantity of residual blood—*i. e.*, diminish the size of the heart.[1]

A distinct recognition of physiological dilatation and physiological incompetency of the valves, apart from the pathological varieties, is of the utmost clinical importance aside from the advantages of precision of thought and precision of knowledge.

I feel quite certain that a clear understanding of these principles will help us enormously to a true conception of cardiac phenomena, whether accompanying organic disease or not. In any given case our first question should be: are the conditions (murmurs, dilatations, irregularity) in part or wholly physiological, and, therefore, in part or wholly, temporary or permanent, curable or incurable? Upon the answer will largely depend both the immediate treatment and the rules for prophylaxis.

[1] Roy and Adami.

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VENOUS THROMBOSIS IN CARDIAC DISEASE.[1]

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One of the most interesting points of view from which to consider the subject of thrombosis is that of its association with different diseases. The study of such association not only is of clinical interest, but is capable of contributing to our knowledge of the causation of thrombosis, which in many respects is still obscure. Infectious and chronic wasting diseases are those most frequently complicated or followed by vascular thrombosis of medical, as distinguished from surgical, interest; typhoid fever and influenza heading the list among the former, and tuberculosis and cancer among the latter. There are, however, a number of other diseases with which peripheral thrombosis may be associated more or less frequently, and to one of these less generally recognized associations I wish to call attention in this paper.

Although there are scattered reports of a number of instances of the occurrence of venous thrombosis in diseases of the heart, I cannot find that particular attention has been called to this complication either in text books on these diseases or in special monographs. This is doubtless attributable mainly to the infrequency of the complication, perhaps also in part to a failure to recognize it. By far the largest number of cases have been reported by French physicians.

As will appear from the following reports of cases, there are certain peculiarities of the venous thrombosis of heart disease which render this subject well worthy of investigation. For the clinical histories of the cases from the Johns Hopkins Hospital I am indebted to my colleague, Dr. Osler.

[1] After its presentation before the Association of American Physicians, this paper was published also in the "Festschrift" in honor of Abraham Jacobi, M.D., LL D., New York, 1900. I have added to the article in its present form Case V., which has necessitated changes in the statistical figures.

CASE I. *Aortic and mitral insufficiency. Adherent pericardium. Broken compensation. Thrombosis of left innominate, jugular, subclavian, and axillary veins. Death.*—R. H., negress, aged seventeen years, admitted November 26, 1898, died January 16, 1899. Nothing of importance in family history or in personal history, until the occurrence, six years ago, of a severe attack of inflammatory rheumatism, with swelling and tenderness of most of the joints. Since then she has not been strong and has had at times rheumatic pains. In January, 1898, occurred a second attack of articular rheumatism, since which she has suffered from shortness of breath on exertion, palpitation, pain in the region of the heart, and some cough. These symptoms became aggravated during the last two months.

Upon admission, patient, who is well nourished, is suffering from respiratory distress. No œdema of extremities. Pulse 112, somewhat irregular, with fair volume and tension. Respirations 40. Temperature 99.5° F. Large veins of neck full and pulsating. Marked bulging of præcordium, and heaving impulse over heart, especially distinct below and outside of left nipple. Marked pulsation in episternal notch. Point of maximum intensity in sixth left interspace, 12 cm. from midsternal line. Relative cardiac dulness begins above in left first intercostal space. Systolic thrill at apex, where on auscultation are heard intense musical systolic and rasping diastolic murmurs transmitted into axilla. In the aortic area both sounds are replaced by a loud to-and-fro murmur, the diastolic portion being especially rough. Second pulmonic sound intensely accentuated. Heart's action irregular and violent. Capillary pulse visible.

At apex of right lung, slight expansion, dulness, prolonged, almost tubular expiration. A few medium-sized moist râles at base of lungs. No tubercle bacilli in sputum.

Liver somewhat enlarged. Urine albuminous, with hyaline and granular casts. Blood count: red corpuscles, 4,524,000; leucocytes, 12,400; hæmoglobin, 65 per cent.

Patient improved somewhat after admission, but her general condition continued much the same. The pulse at times was very intermittent, and there was much tenderness over the præcordial area. The temperature varied from normal to 101° F.

January 14th. For the first time œdema of the left arm is noticed, most marked around the elbow-joint. The right arm is free from swelling. The face and legs are moderately œdematous. Complains of severe headache. Pulse 120, irregular and weak.

16th. Œdema of left arm, which is painful, has increased. Temperature 100.5° F. Pulse very intermittent. Death occurred rather suddenly at 6.30 P.M.

Autopsy by Dr. MacCallum, fourteen hours after death. Body of a girl, rather slenderly built, 162 cm. long. Moderate œdema of ankles and feet. Extensive œdema of left arm, especially about the elbow, the hand being but little swollen. No œdema of right arm and no definite swelling of face or neck.

About 200 c.c. clear yellowish fluid in peritoneal cavity. Surfaces smooth and glistening. Præcordial space greatly enlarged, measuring 16 cm. transversely and 10 cm. vertically. Firm adhesions between parietal pericardium and the pleura, diaphragm, and other surrounding tissues. Left pleural cavity contains over 300 c.c. slightly turbid, yellowish fluid, the left lung being much compressed by this and the enlarged heart. There are many easily torn pleural adhesions. The right pleural cavity contains a small amount of fluid and presents a few light adhesions.

The pericardial sac is obliterated by fibrous adhesions. The heart weighs 720 grammes, and gives the following measurements: right ventricle 8 cm. long, its wall 6 mm. thick; left ventricle 9½ cm. long, its wall 16 mm. thick; tricuspid orifice 10½ cm., mitral 10 cm., aortic 7 cm. All of the cavities much dilated. Left auricle greatly dilated, reaching nearly to first rib. Tricuspid and pulmonic valves delicate. Mitral orifice very wide; valvular segments, particularly the posterior, thickened and retracted. Aortic valvular segments much thickened, stiff, and curled at their edges, so as to be markedly shortened. No fresh vegetations. Coronary arteries patent and free from sclerosis. The aorta shows yellow streaks of fatty degeneration of the intima, and a few small elevated patches of fresh sclerosis.

The left innominate vein, the left internal and external jugular veins, the left subclavian and axillary veins are occluded by a continuous fresh thrombus mass. The prevailing color of the thrombus is dark reddish. The part occupying the innominate just before the reception of the jugular vein and that filling the well-developed bulb of the internal jugular vein is gray or grayish-red, firmer and more adherent to the wall, therefore older, than the dark-red, softer clot in the distal portions. The thrombus in the jugulars stops somewhat below the level of the larynx. The brachial and other veins of the arm are free from thrombus. The tissues around the thrombosed veins are œdematous, and freshly swollen lymphatic glands are present in their neighborhood. The corresponding veins of the right side are free from thrombus.

The lungs are dry, tough, and of a salmon-pink color, evidently the seat of chronic passive congestion. The bronchi contain blood-stained mucus. No areas of fresh consolidation. Pulmonic vessels free from thrombi.

The liver is moderately enlarged, and presents typical nutmeg mottling. Spleen also enlarged, firm, dark red, slightly adherent to surrounding tissues; Malpighian bodies distinct. Kidneys swollen, congested, the seat of chronic passive congestion. Gastric and intestinal mucosæ deeply congested, the solitary follicles swollen. No important changes in other organs.

Microscopical Examination. The swollen lymph glands show marked proliferation of the endothelial cells. The heart muscle is slightly fatty, and shows scattered focal accumulations of small round cells, mainly of the lymphoid type. The kidneys show passive congestion and parenchymatous degenerations, without increase of the connective tissue. The lungs present the usual evidences of chronic passive congestion of moderate degree.

Sections of the thrombosed veins show that the grayish-red part of the

thrombus is composed of platelets, fibrin, and leucocytes with entangled red corpuscles. A coral-like arrangement of the platelet masses is indicated, but is not very distinct. Leucocytes are fairly numerous. There are no evidences of organization. The intima and outer coats contain a few leucocytes, and the intima is somewhat swollen, but there are no signs of sclerosis or other chronic affection of the veins. The redder parts of the thrombus are richer in red corpuscles, but here also islands and bands of platelets and fibrillated fibrin are present. A few chains of streptococci are detected in sections stained by Gram's method.

Bacteriological Examination (Dr. Harris). Plate cultures on agar made with all necessary precautions from the thrombi in the jugular veins showed a considerable number of small, grayish colonies, which were demonstrated to be of Streptococcus pyogenes. No other organism appeared in the cultures. Streptococcus pyogenes was cultivated also from the lungs. Cultures from the heart's blood, œdematous tissue in left axilla, the spleen and other organs were sterile.

The principal points of interest in the preceding case are the following: A girl, seventeen years old, with chronic aortic and mitral endocarditis following acute articular rheumatism, and giving rise to insufficiency of both valves, with relative insufficiency of the tricuspid valve, suffered from the effects of broken compensation. During the last days of life painful œdema of the left arm made its appearance, without implication of the right arm. At the autopsy, in addition to the advanced cardiac lesions and their customary secondary effects, an infectious thrombus was found filling the innominate, subclavian, axillary, and lower parts of the jugular vein on the left side. The oldest part of the thrombus occupied the lower bulb of the internal jugular vein and the adjacent part of the innominate vein. The micro-organism concerned was Streptococcus pyogenes, which was present in the lungs and the thrombus, but was not found elsewhere.

The three following cases are also from Dr. Osler's service in the Johns Hopkins Hospital:

CASE II. *Mitral stenosis. Thrombosis of left jugular, axillary, subclavian, and innominate veins. Embolism of left popliteal artery. Recovery from effects of vascular occlusion.*—E. O., female, aged thirty-five years, admitted January 4, 1899. History of rheumatism in family. Diphtheria at ten, chorea at eleven years of age, accompanied by paralysis of the right side. Since these attacks patient has not been strong. No history of scarlet fever, pneumonia, nor typhoid fever. Obscure history of repeated attacks of "rheumatism" without definite articular symptoms. Patient has suffered for years from shortness of breath on exertion, indigestion, nervousness, and chronic in-

validism. For three weeks before admission has been in bed with epigastric pain and digestive disturbances.

Upon admission patient is very nervous. The point of maximum intensity of cardiac impulse cannot be detected by palpation or inspection, but by the stethoscope is located in the fifth intercostal space, 10 cm. from median line. Area of cardiac dulness not much increased. Very distinct thrill can be felt at the apex, where is heard a rough, intense, presystolic murmur terminating in a short, sharp first sound. No second sound is heard at the apex. Over the body of the heart the valvular sounds are distinct and snapping. The second pulmonic sound is markedly accentuated. Pulse 144, small, irregular both in force and rhythm. Respiration 30. Temperature 99° F.

Medium-sized moist râles are heard behind, over the lower parts of both lungs, where there is also some impairment of resonance.

The absolute hepatic dulness extends from the seventh rib to a point 5½ cm. below the costal margin in the mammary line. The border of the liver can be distinctly felt. There is fairly distinct pulsation of the liver. The epigastric and right hypochondriac regions are somewhat tender to pressure.

There is slight œdema of both ankles. Urine, sp. gr. 1017, contains a small amount of albumin and hyaline and granular casts.

January 12th. The left ankle-joint is swollen, red, and tender.

19th. The left side of the neck is swollen, and painful upon pressure or movement. Temperature 100°. Pulse 124. Respiration 32.

20th. The fulness and tenderness of the left side of the neck have increased, and a sensitive, cord-like body can be felt in the course of the internal jugular vein in its lower part, indicative of thrombosis. The pain and swelling of the left ankle-joint have disappeared. There are evidences of partial consolidation of the right lung below and behind. Moist râles are heard also at the angle of the left scapula. Patient is flighty.

26th. To-day appeared an œdematous swelling of the left arm, extending to the hand. The left arm measures 2 cm. more than the right just above the wrist.

27th. The œdematous, painful swelling is now very marked, and occupies the whole of the left side of the neck, the pectoral region on the left side, the left shoulder, and the left arm to the hand. The œdema has a brawny, indurated character, but there is pitting on pressure. There is no marked difference in the superficial temperature of the two arms. The superficial veins of the arm and neck are distended. On account of the œdema the deeper veins cannot be distinctly palpated. Temperature 101°. Pulse 112. Respiration 40.

31st. The swelling of the left arm is less; that of the neck continues.

February 9th. A cord-like swelling of the left external jugular vein can be traced up to the angle of the jaw. The axillary vein is likewise thrombosed.

26th. The hard œdema of the left arm and neck has continued, at times lessening and then returning. There is œdema of both lower extremities.

March 16th. Pain in the left side and a marked pleuritic friction rub on auscultation.

Soon after this date the general condition of the patient improved, and the œdema of the arm and neck gradually disappeared through the establishment of a collateral circulation.

On November 24th embolism of the left popliteal artery occurred, characterized by loss of pulsation in left popliteal and tibial arteries, sudden pain, numbness, cyanœis, and coldness of the left foot and leg. The history of this embolic attack need not be given in detail. Suffice it to say that a collateral circulation was completely re-established. The patient is still in the hospital.

The diagnosis made by Dr. Osler in this case was mitral stenosis with thrombosis of the left innominate, left internal and external jugulars, left subclavian, and left axillary veins. The location, extent, and persistence of the hard, painful œdema, lasting for nearly three months, make probable the existence of thrombosis of the left innominate and subclavian veins, while that of the jugulars and axillary vein was definitely recognized. The history indicates that the thrombosis started in the lower part of the internal jugular vein. It is to be noted that the onset of the thrombosis was preceded for a few days by a red, painful swelling of the left ankle-joint, and was accompanied by evidences of acute pneumonia and by elevation of temperature, also that during its course acute pleurisy appeared. There is, therefore, much probability in the supposition that the thrombus in this case, as in the preceding, was of infectious nature.

CASE III. *Mitral and aortic insufficiency; general anasarca; thrombosis of the left axillary and brachial veins. Death.*—H. M., male, aged sixteen years, admitted February 24, 1900; died March 8th. No history of infectious disease except pneumonia at seven years of age. Present illness began in August, 1899, with vomiting and indigestion. Says that he had rheumatism in September, but no definite history of affection of joints was obtained. Repeated attacks of gastric pain and vomiting during the autumn. In January, feet, legs, and abdomen became swollen, and he was confined to bed. The dropsy increased, and a week ago the face and hands began to swell. Continued shortness of breath; digestive disturbance continued.

Examination on Admission. Patient is propped up in bed; respiration 32, somewhat labored, and irregular. Cyanosis of face and extremities; œdema of face, thorax, upper and lower extremities, penis, and scrotum; marked œdema of left forearm and hands; ascites. Pulse 124, regular in force and rhythm, fair volume, low tension, hyperdicrotic; pulsation of cervical veins.

Distinct præcordial bulging and general heaving in this region. Apex-beat

in fifth interspace 11 cm. to left of median line; area of cardiac dulness increased, extending 1 cm. to right of sternum and upward to left second rib. At apex first sound replaced by loud systolic murmur heard far out in axilla; second sound faint. In aortic area both sounds enfeebled, the second sound being accompanied by a faint diastolic murmur traceable down along right border of sternum; second pulmonic sound distinctly accentuated.

Physical signs of a moderate amount of fluid in left pleural cavity are present, also some dulness and impairment of respiratory and vocal sounds on right side below and behind, with a few fine moist râles.

Absolute hepatic dulness begins at sixth rib and is continuous with the abdominal flatness due to ascites, which is marked.

The œdema of the left arm and hand is so much greater than that of the right arm that thrombosis was suspected. Upon palpation the left axillary and brachial veins can be distinctly felt as hard, swollen, somewhat sensitive, cord-like cylinders, which can be made to roll beneath the finger.

Blood Counts. Red blood-corpuscles, 6,900,000; leucocytes, 14,600; hæmoglobin, 76 per cent.; 86 per cent. of the leucocytes are polymorphonuclear. Urine contains a small amount of albumin and some hyaline casts; specific gravity, 1027.

After admission the œdema of the left arm and hand continued to increase and reached an extreme degree, so that splits appeared in the corium. The superficial veins were distended. Temperature most of the time a little below normal, only occasionally rising to 99° and once to 100° F.

March 1st. Jaundice appeared. The next day a hemorrhagic eruption appeared over the abdomen. Cheyne-Stokes breathing set in, the sputum became tinged with blood, and death occurred March 8th. Unfortunately, permission could not be obtained for an autopsy.

In the preceding case of uncompensated mitral regurgitation the general dropsy was so great that only the excess of œdematous swelling of the left arm led to examination for venous thrombosis, of which positive evidences were found in the left brachial and axillary veins. Whether other veins were also implicated could not be determined, as no autopsy was permitted.

CASE IV. *Mitral insufficiency; thrombosis of left femoral vein; recovery from effects of thrombosis.*—M. H., male, aged seventy-eight years, admitted December 27, 1898; discharged January 10, 1899. Patient had been in hospital a year ago, suffering from abdominal pain and constipation. At this time mitral insufficiency was recognized. No history of rheumatism or of other infectious disease, except measles and smallpox in childhood. Has suffered of late years from pain in the abdomen, constipation, bronchitis, and increased frequency of urination.

Three days before admission was seized with pain on the inner side of left

ankle and inside of upper part of thigh, soon followed by swelling of the left leg and about the ankle.

On admission a rough systolic murmur is heard at the apex, transmitted to the axilla, and heard also over the body of the heart. Systolic whiff over aortic and pulmonic areas. Point of maximum intensity of cardiac impulse in fifth intercostal space 11 cm. to left of median line. Veins of neck full and heaving, but without distinct pulsation, Superficial veins of nose and cheeks dilated; physical signs of emphysema and bronchitis. Pulse 96, regular; respirations 20. Radial and temporal arteries tortuous and sclerotic.

The left lower extremity œdematous from the groin to the foot, the swelling being most marked around the ankle. Superficial temperature of left leg somewhat higher than that of right; superficial veins dilated. An indurated, sensitive cord can be felt in the left Scarpa's triangle, running obliquely downward and inward. The deep lymphatic glands below Poupart's ligament on the left side are somewhat enlarged. The pulsation of the left femoral artery is less distinct than that of the right; slight œdema of the right leg.

Blood Count. Red blood-corpuscles, 3,800,000; leucocytes, 5000; hæmoglobin, 40 per cent. Temperature remained about normal, occasionally rising in the evening to a little over 99° F. Urine: specific gravity, 1020; acid, faint traces of albumin; no casts.

The œdema of the left leg gradually lessened, and on January 10th patient was discharged at his request with only a little œdema of the extremities.

In the foregoing case there were no marked evidences of disturbed compensation of the mitral lesion, and there was arterial sclerosis. The relationship of the venous thrombosis to the cardiac lesion was not, therefore, so evident as in the three cases first reported, and probably this case does not properly belong in the same category.

For the notes of the following typical, unpublished case, occurring in the service of Dr. James B. Herrick, at the Cook County Hospital, Chicago, I am indebted to the kindness of Dr. H. Gideon Wells, who, when interne at the hospital, observed the patient:

CASE V. *Arterio-sclerosis; mitral and tricuspid insufficiency; fibrous myocarditis and fatty heart; general anasarca; chronic interstitial nephritis; thrombosis of left internal jugular, subclavian, axillary, and brachial veins. Death.*—J C., negro, aged fifty three years, admitted January 10, 1898; died July 24, 1898. History of an old syphilitic infection and of excessive use of alcohol. Patient stated that for three weeks preceding admission he had suffered from pain in the chest, cough, increasing difficulty in respiration, and swelling of the legs and ankles, later of the face, with increased frequency of urination.

Examination showed very marked general anasarca, with slight hydroperitoneum and extensive hydrothorax. The cardiac dulness extended 2 cm.

to the right of the sternum, and 11 cm. to the left of the sternal border; the base reached to the level of the second costal cartilage. There was a mitral regurgitant murmur. The arteries were hard and tortuous; the pulse in the radial and carotid arteries almost imperceptible. Hepatic dulness extended a short distance below the costal margin; the spleen could not be palpated.

The patient remained in the hospital until his death, six and a half months after entrance. During this time he was generally bedridden and suffered from severe dyspnœa, occasional attacks of præcordial pain, and extensive, general anasarca. The urine was loaded with albumin and contained large numbers of casts. At times the amount of fluid in the pleural cavities was so large as to require paracentesis.

About a month before death it was noticed that the left arm was much more œdematous than the right, although there was more than a moderate amount of fluid in the latter. This condition was observed accidentally, being apparently of gradual development, and the patient experienced no pain referable to this trouble. The œdema remained little changed until the time of death, which was the outcome of a gradual cardiac exhaustion.

Autopsy (Dr. S. M. White). Body well nourished. Œdema of all parts of the body, most marked in the left upper extremity, penis, and scrotum. Ulcer, size of a dime, covered by a gray, false membrane, on the left leg.

About four litres of bloody, serous fluid in the peritoneal cavity, the walls of which are thick, white, and fibrous. The left pleural cavity contains about one litre of clear serum, with flakes of fibrin; the right a somewhat smaller quantity. A few fibrous adhesions at apices. The pericardial sac contains about 100 c.c. of serous fluid; a few fibrous adhesions bind the left auricle to the aorta.

Lower lobe of the left lung carnified from pressure; general pulmonary œdema; hæmorrhagic infarction in right lobe. Healed tuberculous nodules in the apices and the peribronchial lymphatic glands.

Coronary arteries dilated and atheromatous. Right auricle reaches 4 cm. to the right of the median line. Right ventricle contains a large, adherent, grayish, ante-mortem thrombus. The tricuspid orifice much dilated. The cavity of left ventricle measures 8 5 cm. in length, its walls 1.5 to 2 cm. in thickness; that of the right ventricle 9.5 cm. in length, its walls 5 to 6 mm. in thickness. Aortic valves normal, save for a few yellowish thickenings at the bases. Mitral segments, thickened, retracted; the orifice wider than normal. Endocardium everywhere somewhat thickened. Papillary muscles mottled with yellowish dots and streaks. Myocardium firm, brownish-yellow, and contains many grayish-white fibrous areas and streaks. Arteries atheromatous, especially the aorta at its beginning and at the origin of the thoracic branches.

The left subclavian vein is filled with a mixed adherent thrombus, in places grayish, but predominately brownish-black, which occupies also the axillary and brachial veins to the middle of the arm. At the beginning of the left subclavian vein is a yellowish, raised, sclerotic area, about the size of a bean,

to which the clot, which here seems to be channelled, is firmly adherent. There is also a thrombus of a brownish-yellow color in the lower end of the internal jugular vein, around which the lymphatic glands are somewhat enlarged and pigmented.

Spleen somewhat enlarged, dark-red, firm. Typical nutmeg liver. Kidneys are the seat of typical arterio-sclerotic nephritis, with adherent capsule, irregular surface, thinned cortex, and obscure markings. Other organs and tissues normal.

Microscopical examination of the thrombus in the subclavian vein showed it to be composed of platelets, fibrin, and blood-corpuscles, with a considerable amount of connective tissue growing into it.

In the foregoing case the cardiac affection was associated with arterio-sclerosis and advanced chronic interstitial nephritis, the patient being fifty-three years of age. The excess of œdema of the left arm over that of the right attracted attention a month before death, but it was unattended by pain or other symptoms. The thrombus apparently started from a sclerotic patch in the left subclavian vein, and was undergoing organization at the time of death.

Thrombosis of pulmonary vessels, which is not particularly uncommon in uncompensated cardiac disease, is of course not to be included in the same class as peripheral venous thrombosis. I have also excluded from consideration the venous thromboses complicating general arterio-sclerosis and chronic nephritis, even when associated with cardiac hypertrophy and dilatation, unless, as in Case V., the symptoms are clearly referable to cardiac disease. Our autopsy records contain five cases of thrombosis of the femoral and iliac veins complicating arterio-sclerosis and chronic nephritis accompanied by cardiac hypertrophy. In two of these there was atheroma of the aortic valves, with some insufficiency. There is one instance of thrombosis of the superior mesenteric veins associated with small kidneys and cardiac hypertrophy. A case of thrombosis of the iliac and femoral veins on both sides, associated with pulmonary emphysema and hypertrophy and dilatation of the right side of the heart, has also been omitted as not falling under the class considered in this article. For the same reason I have omitted a case in our records of thrombosis of the right femoral vein complicating cirrhosis of the liver with sclerosis, calcification, and insufficiency of the aortic valves, and also instances of thrombi in varicose veins in cases of heart disease.

The arterial thromboses complicating cardiac diseases are of much

interest. Doubtless most of those in the systemic arteries are of embolic origin, but there is evidence that some, particularly in cases of extreme mitral stenosis, are autochthonous. This subject, to which I have given some attention in my article on "Thrombosis and Embolism" in *Allbutt's System of Medicine*, does not fall within the scope of the present paper.

The only attempts, which I have been able to find, to collect from the records cases of peripheral venous thrombosis complicating diseases of the heart are those by Parmentier (1889),[1] by Hirschlaff (1893), and by Kahn (1896). Parmentier and Kahn each report a single case from Hanot's clinic, and refer to four others which they say are the only ones they can find in French literature. Hirschlaff adds to Parmentier's list two personal observations and the two cases of Robert (1880) and of Ormerod (1889). Peter, in 1873, in his *Lecons de clinique médicale*, reports a case and devotes a part of one chapter to an interesting consideration of venous thrombosis in diseases of the heart without adding further observations. Huchard's article (1897), "Cachexie cardiaque et thromboses veineuses," and Helen Baldwin's report of a typical case (1897), the only one which I have met in American literature, deserve especial mention. Without pretence to completeness I have been able to collect reports of twenty-three cases to be added to the five observations already described. I have little doubt that a more diligent search would bring to light other reported cases. I shall present in chronological order abstracts of these twenty-three cases, of some of which the histories are very meagre.

CASE VI.—Bouchut (1845). Woman with heart disease succumbed to obliteration of the deep and superficial veins of the left leg. No further details.

CASE VII.—Bouchut (1845). Man with heart disease, in whom occurred obliteration of the superior vena cava, jugular, axillary, and deep arm veins. Engorged, painful, hard, venous cords could be felt in neck and arms. Cyanosis and œdema of face, neck, and arms. Innumerable varicose, agglomerated, large veins appeared in neck and over thorax. A satisfactory collateral circulation developed, and the man left the hospital free from cyanosis and œdema.

CASE VIII.—Cohn (1860). Woman, sixty-one years old. Stenosis and insufficiency of aortic valves, some thickening of mitral segments, cardiac hypertrophy, and symptoms of non-compensation. For fourteen weeks œdema of

[1] The references will be found at the end of this article.

left foot and leg, later also of right foot, but here less marked. At autopsy, adherent old thrombi in both iliac veins, extending on the left side half-way down the thigh, and into some of the larger tributaries of the femoral vein. [Cohn reports two other cases of thrombosis of veins of the lower extremities with cardiac disease, but in these there was general arterial sclerosis and no pronounced valvular lesion.]

CASE IX.—Jolly (1861). Woman with organic disease of the heart had phlegmasia alba dolens of both upper extremities. Death occurred from an ulcero-membranous affection of the intestine. No further details.

CASE X.—Ramirez (1867). Boy, aged twelve years. Acute articular rheumatism one year before admission. Aortic and mitral insufficiency, general anasarca, dyspnœa, and other symptoms of extreme cardiac incompetence. Bloody expectoration. Thrombosis of jugular, axillary, and subclavian veins on the right side. The obliterated external jugular vein very evident. Painful œdema of right side of neck and right arm. Death in coma. No autopsy.

CASE XI.—Ramirez (1867). Man, aged fifty years. For six months following intermittent fever, dyspnœa, general œdema. Incompletely compensated aortic and mitral insufficiency. Œdema of lower extremities almost disappeared, while that of face and upper extremities persisted. Dyspnœa increased. Painful, hard œdema of left arm and left side of neck appeared, and two large, hard, sensitive cords, formed by the obliterated jugular veins, could be felt.

Autopsy showed thickening and retraction of aortic valves, with relative mitral insufficiency. Great dilatation of all cardiac cavities. Blackish, firm thrombi in left internal and external jugular, subclavian, and axillary veins.

CASE XII.—Duguet (1872). Patient, who formerly had acute articular rheumatism, was admitted for dyspnœa, cyanosis, palpitations, and œdema of lower extremities. Three days before death there appeared painful, hard œdema of left arm, and the axillary vein was felt as hard as a cord. Autopsy showed marked stenosis, with insufficiency of the mitral orifice, without fresh endocarditis, with cardiac hypertrophy and dilatation, hydrothorax and hydropericardium, pulmonary infarcts, and grayish-black, non-adherent thrombi filling the left subclavian, axillary, and brachial veins.

CASE XIII.—Peter (1873). Woman with mitral insufficiency and obstruction, and with relative insufficiency of the tricuspid valve, suffered from œdema of lower extremities, ascites, dyspnœa, cyanosis, and great congestion of lungs and liver. For past ten days left arm œdematous throughout, with tenderness at certain points; later outer and lower part of neck became swollen and painful, first near the junction of jugular and subclavian veins. The obliterated subclavian [axillary?] and external jugular veins could be felt as hard, cylindrical cords. Venous pulse, formerly present in cervical veins of both sides, is now evident only on the right side. The left radial pulse is almost imperceptible from pressure of thrombosed veins on the arteries. At the end of three weeks collateral circulation was established

and œdema of arm had disappeared. General condition otherwise unimproved.

CASE XIV.—Robert (1880). Woman, age between thirty and forty years, suffered for eight years with cardiac symptoms following pneumonia, of late palpitation, dyspnœa, cyanosis, œdema of lower extremities and abdominal wall, moderate ascites, pulsation of veins of neck, bronchitis, and pulmonary congestion. Mitral stenosis and relative tricuspid insufficiency diagnosed. For over a month before death patient had increasing œdema of left arm (right being free) and slight tumefaction of left side of face. Left internal jugular vein felt as hard cord; veins over left pectoral region became distended.

Autopsy. Extreme mitral stenosis, with hypertrophy and dilatation of the right heart, double hydrothorax, pulmonary infarcts. Thrombosis of left innominate, subclavian, and both jugular veins. The left innominate was notably narrowed at confluence of jugular and subclavian veins, and here and in the lower end of the jugular was a firm, fibroid, adherent thrombus, evidently the oldest part of the clot. The thrombus elsewhere was in places centrally softened. The walls of the left subclavian vein were thickened. The clot in the jugular could be traced to the entrance of the linguo-facial trunk. Lymphatic glands in the neighborhood of the thrombosed veins are enlarged. Superior vena cava free.

CASE XV.—Parmentier (from Hanot's clinic) (1889). Woman, aged forty years. For four years, following puerperal infection, cardiac symptoms; for last five months, palpitation, dyspnœa, cough, œdema of lower extremities; and for three weeks before admission painful œdema of left arm and corresponding mammary region; later, slight œdema of right arm. Upon admission: very rapid, irregular heart action; irregular, small, intermittent pulse; marked venous pulsation from systolic reflux, intense dyspnœa, pulmonary râles, and albuminuria. The left upper extremity is tumefied throughout its whole extent by a hard, tender œdema, which extends also to the left mammary region. Symptoms increased in gravity and death occurred four days after admission.

Autopsy. Extreme mitral insufficiency and dilatation of all cavities of the heart, left hydrothorax, ascites, nutmeg liver. Left subclavian vein and small communicating veins completely obliterated by a reddish thrombus, grayish and most adherent in the middle of the vein, where it is evidently oldest, and where there is partial organization. Upon microscopical examination the coats of the veins were found thickened and the capillaries in the outer coats dilated. The jugular veins were free, and no thrombus was found in other veins of the extremities.

CASE XVI.—Ormerod (1889). Patient was admitted for mitral stenosis. At autopsy was found complete obstruction by adherent clot of both innominate veins, internal jugulars, subclavians, anterior and external jugulars, the clot being firmer on right than left side. A projecting end of clot hung into superior cava, but was not adherent there, and ceased at the opening of the

azygos. Left auricle and right cavities of heart much dilated. The symptoms of thrombosis, which developed in the hospital, pointed to its commencement in right subclavian vein. No local cause for it could be found. Specimens were presented before the London Pathological Society and no further details are given.

CASE XVII.—Hirschlaff (from Leyden's clinic) (1893). Woman. Repeated attacks during last ten years of articular rheumatism. Cardiac symptoms existed for some time before admission. Upon admission, respirations hurried and labored, œdema of lower extremities, ascites, moist pulmonary râles behind and below, heart's action violent, with diffuse præcordial heaving, cardiac dulness much increased in all directions, loud systolic and diastolic murmurs at apex, feebler systolic murmur, with indistinct diastolic sound in aortic area, distinctly visible venous pulsation; pulse 120, of low tension; enlargement of liver and spleen, moderate albuminuria, diminished excretion of urine. No material improvement followed. Both hands became œdematous. Six days before death there appeared œdema of the left half of the thorax, reaching the middle line, and also of the left supraclavicular fossa; later œdema of left half of face. Pulsation disappeared from the left external jugular, while it persisted in the right. A painful hard cord could be felt in the left supraclavicular fossa, extending upward along the course of the external jugular vein, and a similar one along that of the internal jugular. Erysipelas of the right leg set in after insertion of Ziehl's needles to relieve the œdema, and patient died in collapse.

Autopsy. Extreme stenosis and marked insufficiency of the mitral valve and slighter insufficiency of the aortic valve; cavities much dilated. Thrombosis of the entire left innominate, internal jugular and smaller tributaries, external jugular, subclavian, and axillary veins. The thrombus is reddish-yellow and oldest in the jugular bulb. The veins of the upper arm contained fluid blood; cerebral sinuses free; red induration of both lungs; small quantities of fluid in both pleural cavities; fresh hyperplasia of spleen.

CASE XVIII.—Hirschlaff (1893). Woman, aged fifty-one years. Diphtheria at eighteen; articular rheumatism, without evident sequels, at twenty years of age. For past twenty years epilepsy with periodical swelling of both legs, lasting for months; for last two years persistent œdema of the legs, and for a month before admission palpitation and dyspnœa. Shortly before admission increasing painful swelling of left side of neck and left arm. On admission, marked œdema of lower extremities and of the left side of neck and left arm, slight ascites, slight cyanosis and icterus, systolic pulsation of left external jugular, enlargement of heart, heaving impulse and thrill at apex, loud murmur filling entire period before systole at apex, diastolic murmur in aortic area, dulness and crepitant râles over posterior, lower chest; urine diminished, concentrated and slightly albuminous; pulse 108, small, irregular. The veins in the left side of neck and over shoulder became much distended and the œdema increased in extent. Three weeks later the right side of the neck and thorax, and then the face, became œdematous. Pulmonary symp-

toms. Repeated epileptic attacks occurred, accompanied and followed by extreme cyanosis and dyspnœa. In one of these death ensued a month after admission.

Autopsy. Cardiac hypertrophy, extreme dilatation of right ventricle and auricles; tricuspid valve thickened, its chordæ shortened and grown together; extreme stenosis of mitral orifice, insufficiency of aortic valves, on which are fresh vegetations; myocardium flabby, pale, and yellow. Moderate accumulation of fluid in pleural and pericardial cavities; recent and old pulmonary infarcts; chronic passive congestion of liver, spleen, and kidneys. Thrombosis of superior vena cava, left innominate vein, left subclavian and both internal jugular veins. The oldest part of the thrombus occupies the bulb of the left jugular, where it is firm, closely adherent, and partly organized. Tissues around thrombosed veins behind manubrium sterni œdematous. Small thrombus in the left lateral sinus of the dura mater.

CASE XIX.—Gatay (1895). Woman, aged twenty-eight years. Ten years ago acute rheumatism and endocarditis, followed by palpitation and articular pains. A few days before admission patient was seized with chills, followed by dyspnœa. On admission, cyanosis, œdema of lower extremities, areas of pulmonary consolidation, disorderly action of heart; pulse small and intermittent; albuminuria; temperature 39.8° C. Four days later hard œdema of left arm, most marked in lower part, appeared. Fluid in wrist-joint. Hard venous cord on inner side of left upper arm was felt.

Autopsy. Much hypertrophy and dilatation of heart; the right ventricle markedly dilated and tricuspid valve relatively insufficient; mitral valve thickened, retracted, and incompetent; old fibrous plaques on endocardium; no fresh endocarditis; pulmonary infarcts. Left brachial vein swollen and filled with a red, adherent, centrally softened thrombus, 10 cm. long; venous wall above and below thrombus red and thickened.

CASE XX.—Kahn (from Hanot's clinic) (1896). Woman, aged fifty-two years. Seven years ago, influenza, followed by some œdema of legs, which soon disappeared. For four months before admission, cough, weakness, œdema of legs, loss of flesh. On admission, cardiac hypertrophy, systolic murmur at apex transmitted into axilla; no murmur at base; pulse 100, small, soft; radials sclerotic; external jugular turgid, but without pulsation; respirations rapid and laboried; œdema of lower extremities, emaciation. Ten days after admission painless œdema of right hand and forearm appeared. Temperature, 38.3° C. Subcrepitant râles at base of lungs. The œdema rapidly spread, so as to involve the whole of right arm and corresponding mammary region. There was no pain. The skin was colder than on the left side and somewhat mottled with violet patches. Dyspnœa intense, respiration 42, urine albuminous, sputum bloody, temperature 39° C.; delirium and death in coma about three weeks after onset of thrombosis.

Autopsy. Hypertrophy of the whole heart, right cavities much dilated, mitral valve indurated, thickened, retracted, insufficient without stenosis; other valves normal, fibrous myocarditis. Fluid in left pleura, pulmonary

infarcts, chronic passive congestion of liver and kidneys, spleen swollen and soft. There are five or six enlarged glands near the right subclavian vein, which is completely filled with a reddish, fibrinous, firm, non-adherent thrombus 4 cm. long, extending to the origin of the axillary vein. No thrombi in collateral veins. On microscopical examination, coats of thrombosed vein appear thickened, and capillaries in outer wall dilated.

CASE XXI.—Mader (1897). Woman, aged forty-five years. Repeated attacks of articular rheumatism, followed by palpitation, dyspnœa, and œdema of lower extremities. On admission evidences of stenosis and insufficiency of the mitral and tricuspid valves. Marked ascites. Three weeks later patient complained of great tension in veins of arms; and, in fact, these became enormously distended, as did also the cervical and upper thoracic veins. Collateral veins could be traced to the epigastric veins. There was vertigo, and the lips became cyanosed. With the establishment of a collateral circulation there was gradual improvement in the symptoms. The diagnosis was thrombosis of both innominate veins, possibly also of superior vena cava, complicating the valvular affections mentioned.

CASE XXII.—Helen Baldwin (1897). Girl, aged nineteen years. Three attacks of rheumatic fever, the last seven years ago. Five weeks ago œdema of the feet. A few days before admission, began to suffer from pain in left axilla and left side of neck, also from swelling of the left side of neck. The latter at first would disappear in the erect posture. Amenorrhœa. On admission, great weakness, œdema of both legs, cyanosis, dyspnœa, respirations 40, pupils dilated; pulse 108, small, rapid, and compressible; marked enlargement of heart, double aortic and mitral murmurs, ascites, enlargement of liver, albuminuria, granular and hyaline casts, quantity of urine diminished, sp. gr., 1033. On left side of neck is a hard, tender swelling of lower part of external jugular vein, which is tortuous. There is a hard cord in left axilla, extending for about five inches down the arm. Left arm œ lematous and pale. The next day external jugular vein was felt as a cord up to one-half inch of lobule of ear. Œdema of whole left side of neck. Signs of beginning double pneumonia. For five days there was noted a persistently low temperature when measured by thermometer in mouth, whereas that by the rectum was 6 to 7.8 degrees higher. Bloody expectoration on the fifth day. Death six days after admission.

Autopsy. General œdema, ascites, double hydrothorax, marked hypertrophy of heart, the auricles extremely dilated, chronic changes in all of the valves, the most marked being stenosis and insufficiency of the mitral valve, the edges of tricuspid valve thickened and curled. Pulmonary congestion and infarcts and early stage of double lobar pneumonia. Chronic passive congestion of abdominal viscera. Firm thrombi fill the left innominate, subclavian, external and internal jugular veins, extending nearly to lobe of ear. Veins of extremities could not be further examined. Enlarged lymph nodes along trachea, not pressing on veins. Small extravasation of blood along left side of trachea and behind the left auricle. On microscopical

examination the thrombi were found to be partly organized. There was marked chronic thickening of the intima of the subclavian vein, which was believed to be the starting-point of the thrombus.

CASE XXIII.—Huchard (1897). Woman, aged twenty-four years. Seven years ago had articular rheumatism with cardiac complication, followed by mitral stenosis. Painful swelling of left arm appeared during convalescence from an undetermined febrile disease. On admission severe dyspnœa; pulse rapid, small, irregular; expectoration bloody, urine slightly albuminous, no œdema of lower extremities. Painful, hard œdema of entire left arm, with prominence of superficial veins, and hard, sensitive, voluminous, venous cords. Death in coma nine days after admission.

Autopsy. Double hydrothorax, pulmonary infarcts, slight ascites, nutmeg liver. Heart weighed 450 grms.; buttonhole mitral orifice causing extreme stenosis, slight narrowing of tricuspid orifice, and marked dilatation of right auricle. Large stratified thrombus in left auricle. A few pericardial adhesions. Left brachial vein markedly dilated, and filled in upper part with an adherent thrombus 3 cm. long, starting from a valvular pocket.

CASE XXIV.—Huchard (1897). Male with mitral stenosis and thrombosis of veins of left lower extremity. No other details.

CASE XXV.—Nicolle and Robineau (1897). Girl, aged sixteen and a half years. Repeated attacks of rheumatism during last four years. Chief symptom on admission, respiratory distress; no œdema. Four months after admission patient felt pain in the left side of neck and head, and a hard, painful cord, 5 to 10 cm. long, was detected in the course of the left external jugular vein. Three days later the thrombus had extended and painful œdema of left side of neck and face appeared. Superficial veins dilated; urine slightly albuminous. Ten days after first symptoms of thrombosis entire left upper extremity became œdematous. Œdema increased, and appeared also in lower extremities. Death occurred a little less than a month after the beginning of the thrombosis.

Autopsy. Mitral orifice narrowed, numerous hard, papillary vegetations on borders and surface of mitral segments, also on the aortic valves and the free borders of the tricuspid. Chordæ tendineæ of mitral valve shortened. Hydrothorax, many pulmonary infarcts, pneumonia of left lower lobe. Thrombosis of left external jugular vein and branches and of subclavian vein. Thrombus black, rather soft, slightly adherent, unorganized. Venous walls, especially inner coat, thickened. Swollen, hemorrhagic lymph glands surround the thrombosed veins. Tissues of neck very œdematous.

CASE XXVI.—Poynton (from service of Dr. Lees), 1898. Girl, aged nineteen years. Very severe attack of rheumatic fever, lasting thirteen weeks, nine months before admission. Swelling of legs and abdomen noticed two months before admission, and a few days before admission left arm suddenly began to swell. On admission great pallor and distress, evidences of advanced organic disease of heart, systolic apical murmur, accentuated second pulmonic sound; pulse 90, irregular in force and rhythm; œdema of

legs and thighs, of upper extremities and upper part of chest, the left arm and hand being very much swollen; impairment of resonance and respiratory sounds over bases of lungs, liver large and tender, conjunctivæ icteric, urine somewhat albuminous, temperature subnormal and continuing so throughout illness. Death, preceded by cerebral symptoms and coma, about two weeks after admission.

Autopsy. Totally adherent pericardium, evidences of old rheumatic endocarditis; aortic, mitral, and tricuspid valves incompetent, and mitral orifice slightly narrowed; cavities dilated, especially right ventricle; weight of heart, sixteen ounces. Pleuræ adherent. Chronic passive congestion of viscera. Adherent firm thrombi filled both innominate and both internal jugular veins, the lower end of left internal jugular being white, narrowed, and very firm. Adherent mural thrombosis in upper part of superior cava. Mediastinal tissues œdematous. Brain generally soft and œdematous.

CASE XXVII.—Poynton (from service of Dr. Cheadle), 1898. Woman, aged twenty-one years. In childhood scarlet fever, followed by rheumatic fever. Two years ago second attack of rheumatism. Present illness began gradually with weakness, dyspnœa, and œdema of legs and face. On admission anæmia, œdema of legs, face puffy, bronchitic sounds, harassing cough, systolic thrill, loud systolic murmur over front and back, dilatation of heart. Temperature 101° F.; respirations 28; pulse 128, of low tension. Urine albuminous, sp. gr., 1020, contained blood and casts. Liver and spleen enlarged. Irregular pyrexia and sweating continued throughout illness in hospital. Twelve days after admission pain in wrists and along inside of left forearm. Œdema of face, which had almost disappeared, returned, especially on left side. Irregularity of pulse, orthopnœa, symptoms of renal infarction and pneumonia appeared, and death occurred five and a half weeks after admission.

Autopsy. Heart weighed 14 ounces, all its cavities much dilated; both ventricles and left auricle hypertrophied; muscle pale; mitral orifice widened; numerous exuberant vegetations of mitral segments, also on endocardium of left auricle and left ventricle; chordæ tendineæ ulcerated through; other valves normal, except slight widening of tricuspid orifice. Pulmonary congestion; pneumonia of left lower lobe; chronic passive congestion of abdominal viscera, with infarcts in spleen and kidneys (microscopically no evidence of interstitial inflammation or chronic nephritis). Left internal jugular, from junction with subclavian vein to angle of jaw, occluded by a thrombus, which was pale and adherent to wall, especially in lower part, where vein was cord-like. Innominate vein and right jugular not thrombosed. Brain normal. On microscopical examination no micro-organisms found in cardiac vegetations or in thrombus. Diplococci, staining by Gram, in pneumonic area. Sections of left internal jugular showed organizing thrombus, without distinct thickening of venous wall. Walls of right jugular normal. (No mention of cultures.)

CASE XXVIII. Poynton (from service of Dr. Cheadle), 1898. Girl, aged

nine years. Two years ago scarlet fever, since which heart was affected. For three weeks before admission, thoracic pain and cough, and for one week dropsy. On admission, February 19th, pallor, with some cyanosis; orthopnœa; fingers clubbed; œdema of lower extremities, anterior chest wall and face; some ascites; marked increase of cardiac dulness to right and left; præcordial bulging; epigastric pulsation; systolic and diastolic thrill; double mitral and aortic murmurs; doubtful pericardial friction rub; impaired resonance and respiratory sounds over bases of lungs; scattered bronchitic râles; liver enlarged and pulsating. Temperature 97.4° F.; respirations 30; pulse 100, irregular, weak and small; urine, 1025, contained albumin and blood, without casts. Improvement until March 10th, when pleural friction was heard in left axilla and dulness at left base, without rise of temperature. Again improvement until April 10th, when pulmonary symptoms reappeared and swelling of axillary glands was noticed. Heart more dilated, pulse feebler. 13th: left side of face swollen. 16th: marked œdema of right side of neck, eyelids, and lips; face purple; both sides of neck tense, painful to touch and on movement; temperature subnormal. 17th: right arm began to swell, shortly afterward œdema of left arm and chest; patient apathetic. 18th: drowsiness, cyanosis, sudden dyspnœa, with symptoms of collapse. 19th: tender œdema of right arm extreme. 20th: two firm cords felt in lower part of neck; legs and feet a little swollen; area of cardiac dulness enormous; loud pericardial friction, crepitation over both lungs; urine scanty, slightly albuminous, no blood. Death April 21st.

Autopsy. Acute sero-fibrinous pericarditis; all cardiac cavities dilated and hypertrophied, the right relatively more than the left. Mitral and tricuspid valves incompetent; fresh vegetations on aortic, mitral, and tricuspid valves. Usual visceral changes secondary to advanced cardiac disease. Obliterative thrombosis of superior vena cava in its upper two-thirds, both innominate, subclavian, internal and external jugular, and axillary veins, and the left inferior thyroid vein. Small adherent mural thrombus in left brachial vein. The oldest parts of the thrombus were in the lowest portions of the internal jugular veins and the left innominate, which were white, small, and firm, and adherent to surrounding tissues. Beyond these older thrombi the vessels were bulged with soft clot. The thrombus in the superior cava was soft, pale, non-adherent, except in its upper part.

Cultures and films from pericardial exudate and blood-clot negative; sections of soft clot in superior cava and of thrombus in right axillary showed no micro-organisms. Thrombi were undergoing organization in older parts. Early phlebo-sclerosis, apparently secondary to thrombus, in older thrombosed vessels. Venous wall not thickened where thrombus was fresh and not adherent. Interstitial myocarditis in subpericardial layers and beneath inflamed endocardium.

The most remarkable feature of the foregoing twenty-eight cases of venous thrombosis in heart disease is the location of the thrombi:

twenty-four were thromboses of veins conveying blood from the upper extremities or the neck, or both, mostly of the left side, and only four were thromboses of the veins supplying the lower extremities. I do not suppose that these numbers represent the correct ratio between upper and lower venous thrombosis in heart disease, for thrombosis of veins of the lower extremities in this condition is much more likely to be overlooked in consequence of the more common and greater œdema of the lower limbs, and is also much less likely to be reported. How often it is overlooked can be at present only a matter of conjecture, but it is not probable that such thrombosis is at all frequent. In fact, the comparative infrequency of peripheral venous thrombosis in cardiac disease is in itself a matter of interest, in view of the slow, feeble and irregular venous circulation, and of the frequency of so-called marantic thrombi in the heart itself during the failure of compensation. The relatively small liability to venous thrombosis under such conditions of the circulation is one of many evidences that mere slowing of the blood current is not an efficient cause of thrombosis.

Even allowing for a considerable increase in the number of instances of thrombosis of the veins of the lower extremities as the result of more thorough search in cases of heart disease, the relatively large number of observations of thrombosis of the upper veins revealed in my collection of cases still remains most remarkable. Bouchut places the ratio of venous thromboses of the upper extremity to those of the lower at one to fifty. Of sixty-seven cases of peripheral venous thrombosis in our autopsy records at the Johns Hopkins Hospital, only one was of the upper extremities, although several instances of the latter have been observed clinically in the hospital. Moreover, the four instances above recorded of venous thrombosis of the lower extremities in heart disease had little in common with the remaining cases. Two were in old persons, with some arterial atheroma, and of two no satisfactory history is given. The thrombosis was on the left side in three and bilateral in one, thus conforming to the rule. As will appear from an analysis of the remaining twenty-four cases, the venous thromboses of the neck and arms in cardiac disease constitute a separate and distinct group, characterized by special features of unusual interest.

ANALYSIS OF TWENTY-FOUR CASES OF THROMBOSIS OF VEINS OF NECK, ARM AND CHEST IN HEART DISEASE.

SEX. Seventeen cases were of females, five of males, and of two the sex is not stated. While the total number of cases is too small to warrant percentage estimates, there can be no doubt that females are much more disposed to this form of thrombosis than males. Whether this disposition is more than an expression of the greater liability of females to the mitral lesions present at the ages in the cases observed, I must leave an open question. The figures seem somewhat out of proportion to this greater tendency.

AGE. One patient was nine years old, 6 were between ten and twenty, 3 between twenty and thirty, 3 between thirty and forty, 2 between forty and fifty, 3 between fifty and sixty, and of 6 the age is not stated. Of the 18 patients with thrombosis of the neck and arms whose ages are stated, nearly one-half (8) were between fifteen and thirty years of age. The youngest was nine and the oldest fifty-three.

VALVULAR LESIONS. In 2 cases the exact nature of the valvular lesion is not stated. Of the remaining 22 cases, there was organic disease of the mitral valve in 21; in the exceptional case there was aortic insufficiency with relative mitral incompetence.

The mitral lesion is described as insufficiency in 9 cases, as stenosis in 6, and as stenosis and insufficiency in 6. In the last group there were at least 3 instances of extreme stenosis. The aortic valves were affected in 10 cases, in all of these there being incompetence, sometimes also with obstruction.

The organic valvular lesion was limited to the mitral valve in 12 cases, to the aortic valve in 1, to the mitral and aortic valves in 6, to the mitral, aortic and tricuspid valves in 2, and in 1 case all of the valves were organically diseased.

In all of these cases there was chronic disease of the valves. In five cases there appears to have been a fresh endocarditis engrafted upon the chronic affection, and it is possible that in some other cases this was present, but in the majority of the observations there was no acute endocarditis.

Adherent pericardium was noted in four cases, acute pericarditis in one.

It is evident that the association of thrombosis of the upper veins

with valvular disease of the heart is almost, although not wholly, limited to cases of mitral disease, those of mitral stenosis, with or without insufficiency, taking the lead. The preponderance of females and of patients under middle age is thus, at least in great part, explained. That the complication may occur in men in advanced life with general arterio-sclerosis and chronic Bright's disease associated with cardiac disease is shown by Case V.

RELATION TO RHEUMATISM. As is to be expected from its nature, the valvular lesion was most frequently caused by acute articular rheumatism, of which there was a distinct history in a little over half the cases, but other infectious diseases (scarlet fever, pneumonia, influenza, puerperal infection, diphtheria, syphilis, and chorea) also had a share in the causation. In a number of instances the valvular trouble seems to have developed insidiously. There is, therefore, nothing peculiar in the antecedent histories.

Although several observers regarded the occurrence of the thrombosis as a direct manifestation of rheumatism, only in three cases was there any painful swelling of a joint present shortly before or during the attack of thrombosis.

RELATION TO CARDIAC INSUFFICIENCY. In the great majority of cases the thrombosis appeared during a condition of failure, generally extreme failure, of compensation of advanced mitral disease. The frequency with which pulmonary infarction was observed at autopsy is one of the many evidences of this. Relative insufficiency of the tricuspid valve and pulsation of the cervical veins were noted in many of the cases, and very likely were present in some of those in whose histories they are not noted, but it does not appear that these conditions, although contributory, are necessary factors in the causation of the thrombosis.

LOCATION OF THE THROMBI. A fact which at once arrests attention is that the thrombosis affected veins of the left side in 22 out of the 24 cases, of which 15 were unilateral and 7 bilateral. In only 2 cases were veins of the right side alone affected. Bilateral thrombosis is, therefore, more common than unilateral right-sided thrombosis, and unilateral left-sided thrombosis is by far the most common form of the disease. The hypotheses in explanation of this distribution will be considered later.

In 7 cases the thrombosis was apparently limited to the arm veins.

in 1 to veins of the neck, and in 16 cases veins both of the neck and arms were thrombosed. In 1 case the thrombus was confined to the left subclavian vein, in 1 to the left internal jugular, and in 2 to the left brachial. In all the other cases more than one vein was thrombosed, the combination varying in different cases, the most common being continuous thrombosis of the left innominate, internal and external jugular, subclavian, and axillary veins. The superior vena cava was partly or wholly thrombosed in 6 cases (confirmed by autopsy in 4), the innominate in 11 (confirmed by autopsy in 8), the internal jugular in 14 (autopsy in 11), the external jugular in 12 (autopsy in 8), the subclavian in 16 (autopsy in 13), the axillary in 11, the brachial in 6, the inferior thyroid in 1, and the left lateral sinus of the brain in 1.

The commonest starting-point for the thrombus was the lowest part of the left internal jugular (bulb), or of the left external jugular vein and the left innominate or subclavian vein near the entrance of the jugulars. In many cases this was clearly demonstrated by the appearances of the thrombus and the venous wall in these situations. The thrombus may, however, originate in other veins, especially in valvular pockets of the veins in the left arm.

The most extensive thrombosis was that recorded by Poynton (Case XXVIII.), in which there was occlusion of the superior vena cava in its upper two-thirds, of both innominate, internal and external jugular, subclavian, and axillary veins, and the left inferior thyroid vein.

The thrombus was generally a continuous one, apparently originating in one vein, whence it was propagated into peripheral veins and also centrally, even into the superior vena cava.

Characters of the Thrombi and Venous Walls. The thrombi were mixed, the prevailing color being dark red. The older parts were gray or reddish-gray and adherent. The fullest description of the microscopical characters is that which I have recorded under Case I. In a few instances the thrombus was centrally softened, but in most it was solid and completely occluding except at the ends and except in the mural thrombus mentioned in Case XXVIII. The older thrombi were usually more or less advanced in organization. Bacteria were searched for in apparently only 3 cases, and were found only in my Case I., the organism here being Streptococcus pyogenes.

In 7 cases it was noted that the wall of the thrombosed vein was

thickened, but this thickening was generally regarded as secondary to the formation of the thrombus, which was two or more weeks old. Only in Helen Baldwin's case and in Case V. is it distinctly stated that the appearances indicated phlebo-sclerosis (subclavian vein) antedating the thrombus. In two of Poynton's cases the jugular and innominate veins, where the oldest part of the thrombus was situated, were narrowed, white, and firm, and a similar condition was noted by Robert. Chronic disease of the veins evidently plays only a minor part in the causation of the thrombosis in these cases.

Effects and Symptoms. The anatomical lesions outside of the vessels directly referable to the thrombosis were œdema of the tissues and swelling of the lymphatic glands. The œdema cannot always be explained entirely as the result of venous congestion, but is in part inflammatory, as is true in general of the œdema in phlegmasia. Swollen lymphatic glands, which were sometimes hemorrhagic or pigmented, were often observed in the neighborhood of the thrombosed veins. This swelling was generally acute and evidently secondary to the thrombosis, but Kahn attributed the exceptional localization of the thrombus in the right subclavian vein in his case (XX.) to the pressure of previously enlarged glands. Poynton noticed cerebral œdema in one of his cases which had manifested brain symptoms.

The local symptoms are the usual ones of venous thrombosis: pain, tenderness, œdema, the presence of hard, sensitive venous cords, and distention of superficial veins. Often the pain, sometimes the œdema, was the first symptom. The œdematous swelling may be hard and brawny, or softer, as in dropsy. In some cases the pain and œdematous swelling were first manifest in the neck, in others in the arm. Extension of the œdema to the front and side of the upper part of the thorax was repeatedly noted. Occasionally the side of the face corresponding to the thrombosis was œdematous. The extent and distribution of the œdema, while dependent in the first instance upon the extent and location of the thrombosis, were influenced, as is usual in venous thrombosis, by other factors, so that they varied much in cases with the same distribution of the thrombi.

Constitutional symptoms of the thrombosis, if present, could not readily be separated from those of associated conditions. The marked difference between the buccal and rectal temperatures observed in Helen Baldwin's case (XXII.) is interesting. Cerebral symptoms,

attributed by Poynton to cerebral œdema, were observed in a few cases.

As is illustrated by Case V., the only symptom of the thrombosis may be œdema, usually of the left arm, the patient suffering little or no inconvenience from the swelling, and the affection being recognized sometimes almost accidentally.

Hanot, in 1874, called attention in a short note to the more rapid onset and the longer persistence of œdema of the left arm, as compared with the right, in cardiac affections, and he explained this peculiarity by the greater length and obliquity of the left innominate vein. It would appear, therefore, that œdema limited to or in excess in the left arm in heart disease should not be regarded as positive evidence of thrombosis of veins conveying blood from this extremity. While this is doubtless true, it is desirable, in view of the cases reported in this paper, to search carefully in these instances for other evidences of thrombosis.

PROGNOSIS. Of the twenty-four cases, twenty ended fatally and four (Cases II., VII., XIII., and XXI.) recovered. The gravity of the prognosis doubtless mainly results from the circumstance that the occurrence of the thrombosis is in itself an index of extreme failure of compensation of the valvular lesion, being sometimes scarcely more than a terminal event. We know that occlusion of the superior vena cava and its large tributaries, due to other causes, may be completely compensated by the development of a collateral circulation, and there are instances of this even in the present group of cases (VII. and XXI.), so that it is less the venous occlusion than the condition of the heart and the frequent presence of pneumonia or other terminal infections which makes the issue so unfavorable. In rare instances, thrombosis of the upper veins may occur at a period when the compensation is not badly broken (Case II.). Large pulmonary embolism was not observed. Whether pulmonary infarcts, which were frequently present, were attributable to emboli derived from the venous thrombi was not determined. The duration in the fatal cases of thrombosis varied from two days to six weeks.

CAUSATION. Although five of the cases were reported as instances of rheumatic phlebitis, it does not seem to me demonstrated that even in these cases (XII., XIX., XXVI., XXVII., XXVIII.) this was the correct explanation, and it is certain that the great majority of cases

cannot be explained in this way. It is true that phlebitis, or venous thrombosis, is a genuine, although infrequent, complication of acute rheumatism, and there is some evidence that it may affect veins of the upper extremities somewhat more frequently than does thrombosis due to most other causes, but there is no such enormous preponderance of upper thromboses as in the class of cases now under consideration. As alreaded mentioned, the histories of the cases do not support the view that rheumatism had more than a minor share in the immediate causation of the thrombosis. There is no reason, however, why acute rheumatism, like other infections, may not directly participate in the causation of the venous thrombosis.

French writers (Peter, Parmentier, Kahn, Huchard) attribute the thrombosis to cardiac cachexia combined with circulatory disturbances. They say that this cardiac cachexia (so designated by Andral) is something to be distinguished from asystole—that is, from mere breakage of compensation. They bring this class of thromboses, therefore, into line with that complicating tuberculosis and cancer, and explain the peculiar localization by the particular disturbances of the circulation in cardiac disease. The underlying cause, according to this view, is some alteration in the chemical composition of the blood. It is difficult to say how much weight is to be attached to this explanation. In many cachectic conditions there is an increase in the blood platelets, attributable probably to weakened resistance of the red corpuscles, and some writers have brought cachectic thromboses into relationship with this increase. According to van Emden, the number of platelets is diminished in the chronic congestion of heart disease. I know of no observations concerning the number of platelets in these cases of heart disease with venous thrombosis. I could find nothing in the histories of most of the cases indicating any peculiar cachexia, and I am not inclined to regard this explanation of the thrombosis of heart disease as a satisfactory one.

The first thing which needs explanation is the localization of the thrombosis in the veins receiving blood from the upper part of the body, and especially from the left side. Hanot and Parmentier explain the preference for the left side by the greater length and obliquity of the left innominate vein, so that, like the return flow of blood from the left leg, that from the left arm and left side of the neck is more difficult than from the right side, this difficulty being, of course, most in evidence in the venous congestion of uncompensated cardiac

disease. Hirschlaff suggests that an additional factor may be the greater frequency of imperfect development and of insufficiency of the valve near the junction of the internal jugular and subclavian veins on the left than on the right side. To these factors I would add pressure, either direct or indirect, on the left subclavian vein from the dilated left auricle and dilated large pulmonary vessels. Popoff noted pressure from this source on the left subclavian artery in mitral stenosis with insufficiency as a cause of relative weakness of the left radial pulse (pulsus differens). I would refer to his article for a consideration of the factors concerned in producing this pressure. A large accumulation of fluid in the left pleural cavity, which was noted in many of the cases, may also contribute to this pressure.

Peter, in 1873, was the first to suggest that the frequency with which the thrombus starts from the lower ends of the jugulars is to be explained by the presence of valves in this situation. I am inclined to lay emphasis upon the readiness with which an eddying or whirling motion of the blood may be set up in heart disease in the lower ends of the jugulars and the adjacent parts of the innominate and subclavian veins. Von Recklinghausen has brought forward strong evidence that this whirling movement (Wirbelbewegung) of the blood is of great importance in determining the localization of thrombi in general. The valves, the bulbous enlargement at the lower end of the internal jugular, the attachment of veins to fasciæ, and the coming together here at oblique and right angles of currents of blood with different pressures and velocities, seem well calculated to cause in these veins whirling or vortical motion of the blood current, especially in the circulatory conditions of broken compensation of mitral lesions. Most favorable to this peculiar disturbance of the circulation would be tricuspid insufficiency with systolic reflux of blood into the veins. I would explain, therefore, the special localization of the venous thrombosis complicating cardiac disease, on the one hand by the particular disturbance of the circulation, and on the other by the anatomical disposition and structure of the veins.

These factors, however, explain only why certain veins are the seat of election for the thrombi. The circulatory conditions described must often exist within these veins in uncompensated cardiac diseases, whereas venous thrombosis is a rare complication of heart disease. In the case which first directed my attention especially to this subject, and which I have here reported as Case I., an immediately exciting

cause for the thrombosis was discovered by the demonstration of bacteria in the thrombus. This is the only case in the entire list in which micro-organisms were found, but, so far as I can gather, in only three other cases were bacteria especially looked for, and it does not appear that in any of these latter were cultures made from the thrombus. Such cultures are, of course, necessary in order to exclude the presence of bacteria, and, indeed, our experience has been that even a negative result from cultures is not absolutely decisive. Evidence has accumulated in recent years in support of the infectious origin of many thrombi. Dr. Harris and Mr. Longcope, who will report their observations later, have now examined in my laboratory bacteriologically forty-four thrombi, mostly peripheral venous thrombi of the so-called marantic type, and in thirty-four of these have demonstrated the presence of bacteria. As has been shown by Dr. Flexner in my laboratory, terminal infections are not uncommon in heart disease. The histories and autopsies of many of the twenty-four cases now under consideration revealed some infectious process, usually in the lungs, such as bronchitis, pneumonia, and pleurisy. While, therefore, it would be quite unwarrantable, from existing evidence, to refer this class of venous thromboses in cardiac disease positively to infection, this seems to me at present the most probable explanation.

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DISCUSSION.

DR. KINNICUTT: The lesion which Dr. Welch has described occurred in a patient under my personal observation. A gentleman, fifty-eight years of age, suffering from mitral stenosis and insufficiency, suddenly developed swelling of the left upper extremity, with pain and sensitiveness along the course of the branches of the brachial plexus above the elbow. In the course of twenty-four hours the swelling extended to the left side of the neck and face as high up as the ear. The patient's condition was a grave one for several days, but recovery occurred with the establishment of an imperfect collateral circulation. Fair health was enjoyed for ten years, when a thrombosis of the perineal vein suddenly occurred, from which at the present date he was slowly recovering.

DR. CARY: I had a case of this kind just before leaving home, thrombosis starting in the internal saphenous vein and involving finally the superficial veins of both upper extremities. I would like to ask if, in addition to the mechanical causes suggested by Dr. Welch, he does not regard pressure on the superior vena cava by the left auricle as an important factor? For it is certainly true that the left auricle is dilated in all cases of true mitral obstruction, and its relation to the cava would cause obstruction in veins rather than below the heart.

DR. BIGGS: I would like to speak of a case which shows all the characteristics described—a young woman, whose age I do not remember, something over twenty years—with mitral insufficiency and broken compensation developed, one month after coming under observation, extensive œdema of the left arm and of the surface of the chest and left side of the neck. She had very severe pain in that side. She lived about four weeks, and at autopsy we found thrombi in the left internal jugular, the left innominate, and left subclavian. The oldest portion of the thrombus was situated in the bulb of the internal jugular, as shown by softening there. It seems to have been a case exactly similar to those described in Dr. Welch's paper,

DR. WELCH: I am not surprised to find that members of the Association have observed cases similar to those which I have reported, for in bringing this paper before the Association I felt quite sure that other instances of this complication of cardiac disease would come to light. Dr. Janeway has told me to-day that he has seen three such cases, and I anticipate that reports of venous thrombosis in heart disease will follow the publication of this paper. It seems remarkable that this interesting and peculiar type of thrombosis should not have received attention in text-books on diseases of the heart.

I omitted, in condensing my paper in its presentation to you, the part in which I consider the influence of dilatation of the left auricle in favoring the occurrence of thrombosis, and I will now read the sentences relating to that point. (These were read.)

A CASE OF MULTIPLE FIBROMATA OF THE NERVES, WITH ARTHRITIS DEFORMANS.

By ROBERT B. PREBLE, M.D.,

AND

LUDVIG HEKTOEN, M.D.,

OF CHICAGO.

Clinical History (Dr. Preble). The patient, female, J. S., aged thirty-five years, comes from a healthy family. The parents are living and in good health. One grandfather suffered from rheumatism and died in advanced years. The other grandfather died of dysentery contracted in the Rebellion. One grandmother is living and in good health, considering her age. The other grandmother died of some disease unknown. In short, the family history presents nothing of interest—especially is there no history of any tumors in any way resembling the tumors presented by the patient.

When very young a tumor appeared on the forehead and grew slowly to about the size of a pigeon-egg. Because of the disfigurement, effort at removal was made by a doctor, who, to judge from the account of the friends, performed some sort of a morcellating operation, rather than make any attempt at radical removal. Shortly after this other tumors appeared irregularly and in great numbers over the entire body.

The patient passed through many of the ordinary diseases of childhood, and reached young womanhood without any other abnormality than the tumors to be described later. But gradually she began to suffer from pains and weakness, which gradually increased until they caused complete disability.

She gives a history of a complete paraplegia without bladder or rectal disturbances, which ceased spontaneously long before she was examined by me. From the history given, I am inclined to believe that the paraplegia was hysterical.

Some years after the appearance of the tumors, but just when neither she nor her friends can recall, she began to show the beginnings of the joint changes which are now so marked. These consisted of swelling and deformity, but there was not much pain. The joints first and most involved were the smaller joints of the hands; the changes began symmetrically.

The tumors have not caused much disturbance, as a rule; some few of them

have, however, been painful. The patient insists that they vary in size from time to time, and that some have entirely disappeared spontaneously. This has been noted mainly on the hands. Some two years before I saw her one of the tumors on the left thigh, high up on the posterior surface, ulcerated, and in spite of every care and manner of treatment the ulcer has never healed. The patient was seen first in 1894, complaining of abdominal pain, described as drawing in character and tending constantly to pull her forward. She complained also of pains in her legs and feet. It was extremely difficult for her to get from her bed to her chair, and walking was impossible. The ulcer on the thigh was painful and troublesome. This, briefly, was her complaining.

Examination shows a small, emaciated and deformed woman, looking many years older than thirty-five. The mind is clear, and the intelligence fair, although she is irritable and unreasonable, as one might expect in one confined to her room for years with so painful and distressing an illness. The skin is pale, and without any areas or flecks of pigmentation. It is marked by many tumors which vary in size and appearance. Over the forehead are small tumors up to the size of a small bean, arranged in irregular and tortuous strings, so that they give through the skin a sensation not unlike that of a scrotal varicocele. They are not painful or tender. They extend not only across the forehead but back also into the hair. There are other tumors on the face, but none presenting this racemose arrangement. The tumors of the skin over the neck, body, and limbs vary in size from a large pin-head to the size of a nut. Some are sessile, some are pedunculated. They are covered usually by a thin and wrinkled skin, although some of them are quite smooth and shining. None are pigmented or hairy. None are painful.

In addition to the tumors of the skin we find others in the deeper parts, fusiform or ovoid tumors, which show a disposition to arrange themselves parallel to the long axis of the neck or limb. They permit of lateral but not of longitudinal motion. They vary in size up to that of a large potato. They are not attached to the skin, which is in no way altered. With the exception of one in the neck they are not painful.

On the posterior surface of one thigh is an ulcer about half an inch in diameter and more than that in depth. The borders are sharply marked, and although every effort has been made to favor healing, the ulcer has not improved in months, nor did it ever improve. It looked exactly like the perforating ulcers seen on the feet of patients suffering from tabes.

Examination of the hands shows very great deformity. The deformity is symmetrical and began in the smaller joints. The joint surfaces are entirely destroyed and the capsule so relaxed as to allow motion in all directions. The resulting deformity is as great as is seen in a well-marked arthritis deformans, but it is not exactly like that seen in a typical case. The wrist-joints are similarly affected. The knee- and hip-joints are anchylosed. Motion of the jaw is limited, and there is considerable deformity of the spine.

The organs of the thorax and abdomen presented no variations from the

normal and were performing their functions perfectly. The blood showed a moderate reduction in the percentage of hæmoglobin, but otherwise was normal.

Pelvic examination under anæsthesia showed a virgin uterus which was normal in all respects. High up in the pelvis and abdomen there were tumors which exactly resembled those seen on the limbs.

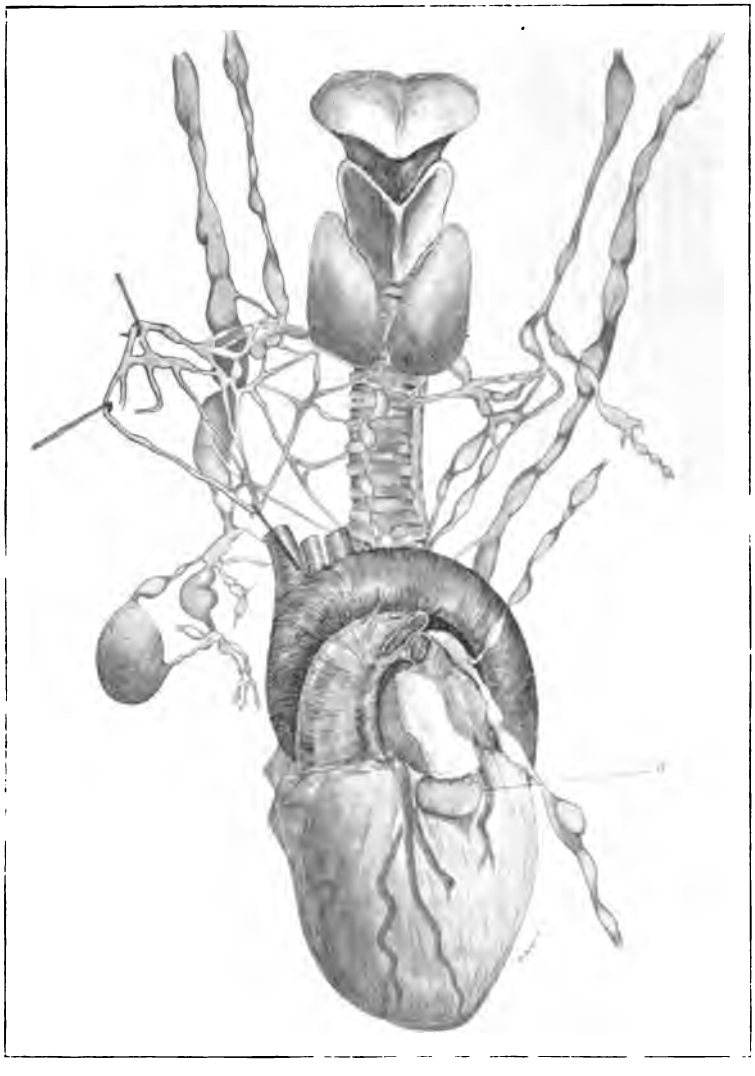
The nervous system presented no alteration whatever. All of the cranial nerves were in perfect condition. All of the elements of the sense of touch were perfect. There were no paralyses anywhere. The leg reflexes could not be examined because of the anchylosis of the joints.

As time went on the patient became more and more wretched. Against the advice of the physician, she was supplied with morphine, and became a morphine fiend. There was no essential change in her condition except for the rather rapidly increasing deformity of the spine, the kyphosis increasing until the chin almost came in contact with the pubes. She continued to amuse herself, as she had for years, by making little trinkets and fancy articles, doing this in spite of the deformity of the hands. No essential change in her condition occurred except for a peculiar thickening of the skin of the leg. The pain in the abdomen and legs continued. No paralyses or disturbance of the bladder or rectum appeared. About ten days before death gangrene of the toes of the left foot appeared. Her pain became more severe, and death occurred without any apparent definite cause.

Post-mortem Examination (Dr Hektoen). Female body, five feet three inches, slight rigor, extreme and uniform emaciation; the body is greatly deformed on account of a marked kyphoscoliosis, whose greatest curve lies in the lumbosacral spine, with its convexity to the right and backward; in the cervical region is a smaller curve with the convexity to the left. The knee-joints are fixed at right angles, and the head of the tibia partly dislocated backward. Both hip-joints are immobile, and the thighs are flexed on the abdomen. The shoulder- and elbow-joints are stiff. The left wrist-joint and the right ulnocarpal joint are apparently completely disorganized and flail-like; also the joints of the thumbs, the distal phalanges of which are flexed outward at right angles. There is palmar dislocation of all the phalanges of both hands, more marked in the left. The phalangeal joints of the first and fourth fingers of the right hand are flail-like—second and third fingers are not changed. The small joints of the left hand are changed to less degree. The nails of the fingers are not changed. The ankle-joints and the joints of the feet are changed in a similar manner. The skin of the toes of the right foot is dry, covered by scales, toe ends glossy, the nails greatly thickened and furrowed. The toes and dorsum of the left foot are the seat of a moist, foul gangrene. Upon the inner surface of the right leg is an oval area of furrowed, horny thickening of the skin, raised 5 mm. above the general surface, 6 x 3 cm. in extent. Over the tuberosity of the right ischium is a deep, oval sore.

The skin shows also innumerable tumors, varying in size from a pin-head

FIG. 1.



Showing tumors of pneumogastric and cervical sympathetic nerves and their branches. At *a* subpericardial tumor nodule.

FIG. 2.

Tumors of sciatic nerves and their branches. At *a* large tumor connected with small intermuscular nerve.

to a pecan-nut, quite movable and unattached to deeper structures, some barely raised above the surface, some almost pedunculated. Over some the skin is smoothly drawn, over others it is lax and wrinkled; they are either round and globular or oval and flattened; in many places they show a disposition to arrange themselves in lines; in the forehead and scalp they have a plexiform arrangement; they are probably most numerous in the skin of the face and neck, the largest one being situated in the subcutaneous tissue of the right side of the neck; they are also very numerous in the skin of the hands, especially the right; over the trunk they occur quite richly, occurring in parallel lines along some of the ribs; the skin of the legs contains the smallest number.

The peritoneal cavity is empty, its lining smooth and shining. The stomach is more vertical than usual, the lowest limit of the large curvature reaching below the umbilicus; the cæcum and vermiform appendix lie in the true pelvis, pressing the uterus and ovaries against the lateral and anterior walls and the bladder; the transverse colon describes a large curve, the convexity reaching to the lowermost part of the cavity. The diaphragm reaches to the fifth rib on both sides.

Both pleural cavities are empty, the pleuræ smooth. The right pleural cavity becomes very small in the lower part. Running along the lower edge of some of the ribs are extrapleural rows of small nodules.

The phrenic nerve presents a few small cylindrical enlargements as it runs over the pericardium, which is empty and smooth.

There is no fat in the subserous tissue anywhere.

The tongue, pharynx, and œsophagus are quite normal. The larynx and trachea are also normal. The thyroid is normal in size, the thymus absent.

The lungs crepitate; they are rather light and spongy; the cut surface is not much pigmented and is rather bloodless; there is no bronchitis; the peribronchial lymph glands are not enlarged.

The pericardium is smooth; in the subpericardial tissue of the anterior surface of the left ventricle, just below the auriculo-ventricular sulcus, lies a rounded mass, 1.5 x 7 cm , over which the epicardium is a little roughened (Fig. 1). The heart is small, the coronary vessels convoluted, the myocardium brownish, the endocardium smooth.

The spleen is of the usual size and free from changes.

The liver is small, has a nutmeg-cut surface. The gall-bladder is empty. In the mesentery appear many small, whitish, flattened and oval firm bodies, many of which are in the direct course of small nerves. In the part near the root are softer, yellowish masses as large as split pease or so. The mesenteric attachment of the duodenum contains several pairs of small bodies closely together, one of which is whitish and rather firm, the other more yellowish and rather soft. The serous covering of the duodenum has numerous slightly raised patches of irregular outlines and of a peculiar saffron color; it is in general somewhat thicker and rougher than normal.

The stomach contains a quantity of blackish fluid; in the fundus an ex-

tensive district of the mucosa has been digested, and a small part of the wall is so soft that it ruptures on handling; otherwise the gastric mucosa is quite normal. The mucous membrane of the duodenum and jejunum contains a few irregular districts which are finely nodular to the feel, the membrane being somewhat granular to the eye. The ileum and the large intestine are quite normal, the latter containing masses of soft, yellow feces, the former being empty.

The nerves of the retroperitoneal tissue, including those radiating from the splanchnic ganglia, present closely aggregated beaded enlargements varying in size from a pin-head to a bean. The nerves in the pelvis behind the peritoneum present numerous globular and oval enlargements up to the size of walnuts, of a similar glistening and whitish appearance. Situated upon the inner surface of the left side of the upper half of the sacrum is a firm spherical mass as large as a pigeon-egg, which is deep bluish-black in color with a few gray spots, and which has a somewhat reticulated cut surface. The deep and superficial inguinal glands, especially on the right side, are pseudomelanotic and somewhat enlarged as well as quite firm.

The adrenals are normal in appearance, the right being rather flattened; there are no tumors in their immediate vicinity. The kidneys are small, the capsules free, the surface slightly granular in places and rather yellowish. The cortical markings are somewhat indistinct. The pelves, ureters, and urinary bladder normal. The ovaries and uterus are small; otherwise no changes.

The subcutaneous tissue of the scalp contains tangled, cord-like masses of thickened nerves both in the frontal and occipital regions; in many the thickening seems diffuse, in other cases small white tumors spring from the epineurium.

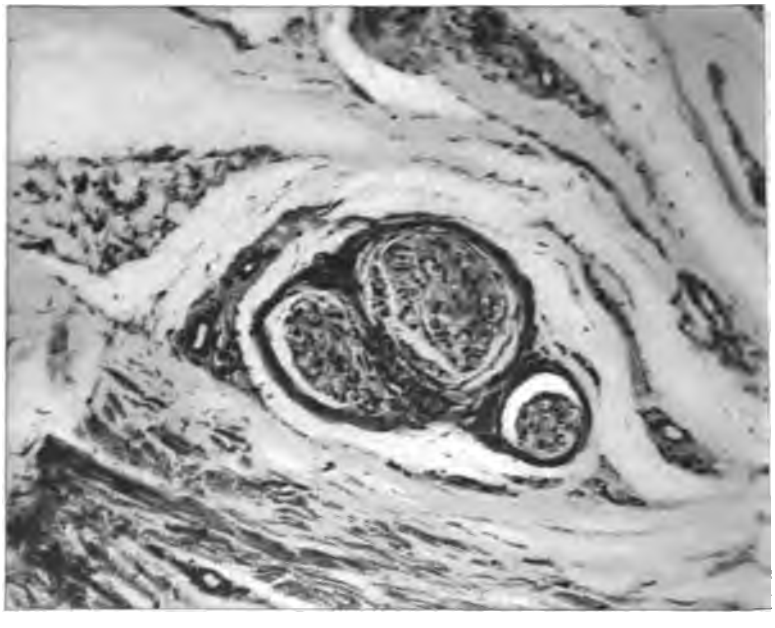
The skull is of moderate thickness but increased density. The skull form symmetrical. The dura is smooth. The pia contains a moderate amount of clear fluid. Externally the brain and the intracranial portion of the cerebral nerves are normal. The brain is hardened unopened in formalin solution. The right optic nerve and the right globe and motor nerves show no changes. The hypophysis is of about normal size, the cella turcica is rather deep. The sphenoidal sinuses are empty and smooth. The frontal sinuses are covered with a layer of dirty, grayish, thick fluid.

On account of the spinal curvature it is rather troublesome to remove the spinal cord, which seems of natural size; its membranes are smooth. Upon three or four of the lower dorsal nerves are small fusiform enlargements of the intraspinal portions. Upon each of the third and fourth right cervical nerves is a smooth, glistening, cylindrical enlargement, located within the spinal canal underneath the pia (Fig. 8); there are numerous similar enlargements in the course of the nerves outside of the canal; the larger of the intraspinal tumors is 3 by 1.5 cm., smooth and white, and presses the cord to one side; coursing over its surface are small, apparently healthy nerve bundles.

FIG. 3.

Skiagraph of left hand, showing absorption at articular ends and surface. (Courtesy of Dr Smith, X-ray Laboratory, Presbyterian Hospital.)

FIG. 4.



Chronic fibrous neuritis of small cutaneous nerve of left index finger. Hematoxylin and eosin. × 150.

The spinal cord and brain are hardened as a whole in 4 per cent. formalin (see below).

In addition to the tumors in connection with the nerves already referred to, it is found that, generally speaking, every nerve of the neck, trunk, and lower extremities is the seat of numerous and variously sized globular or oval, firm growths. Thus both pneumogastrics and their connecting and other branches carry innumerable tumors that appear to spring from the peri- and endoneurium; the large trunks contain so many small tumors in their interior that they appear as if diffusely enlarged, the larger masses giving rise to nodules in the course of the nerve (Fig. 1). In the smaller branches the relation of the tumor to the sheath is often clearly shown, the nerve running over the tumor. One of the œsophageal branches presents a globular growth as large as a walnut, which presents upon the gullet and causes a narrowing of the lumen.

The sciatic nerves, which were hurriedly dissected out, together with the tibial nerves, present a similar well-marked diffuse nodular enlargement of the main trunks, which appear at least four times the normal size (Fig. 2); this great enlargement is largely due to the presence of tumors in the nerves, but here there also seems to be a diffuse overgrowth of the structures. The largest tumor of all is a cylindrical mass, 12 by 3.5 cm., situated loosely between the muscles on the anterior part of the right thigh and connected with a small intermuscular branch. The larger nerve trunks of the upper extremities are not dissected out, but feel markedly nodular on palpation.

The following joints were examined: The left wrist-joint, the metacarpo-phalangeal joints of the left hand, the right knee- and hip-joints. The right hip-joint is empty and the articular surfaces held in such close apposition by the thickening of the ligaments that partial anchylosis exists. The articular cartilages are thinned and somewhat roughened, but there is no distinct erosion and no marked osteophytic formations. The head of the femur is reduced in size. The knee-joint contains a small quantity of clear viscid fluid, in which are small grayish turbid masses. The synovial fringes are changed into a soft, reddish and granular tissue; surrounding the articular cartilages, which are thinned and roughened, are extensive erosions of the bone, in which lies a sort of granulation tissue that seems to be in direct connection with the red marrow that fills the medullary spaces; extensive resorption of the upper end of the tibia has taken place; the capsule and ligaments are thickened. Generally speaking, similar changes are present in joints of the hand and wrist (Fig. 3). The extensive resorption furrows around the articular bone ends are especially well marked; there is considerable clear viscid synovial fluid with gray flocculi, also soft masses of tissue on the synovial membranes, and thickenings of the capsules. There is probably some new bone at the margins of the grooves at the bone ends.

The marrow of the long bones is red.

Anatomical Diagnosis. Multiple fibromata of the cerebro-spinal and sympathetic nerves; compression of the spinal cord; polyarthritis deformans with

kyphoscoliosis, anchyloses, and contractures; moist gangrene of left foot; decubitus; chronic dermatitis of left leg; inflammation of frontal sinus; chronic nephritis; marasmus.

BACTERIOLOGICAL EXAMINATION. Cultures made from the heart's blood, all the solid organs, and four sets of five tubes each of blood-serum inoculated with the contents of various joints; two tubes of human placental blood serum inoculated with the same material.

Cover-slip preparations from the synovial fluids and from the synovial tissues stained in a great variety of ways do not show any micro-organisms, and all the cultures from the joints remain sterile.

A non-liquefying micrococcus, which takes Gram's stain and shows a marked tendency to arrange itself in fours, was isolated from the heart's blood and the spleen. The lungs contained the proteus vulgaris, the liver the colon bacillus; the kidneys were sterile.

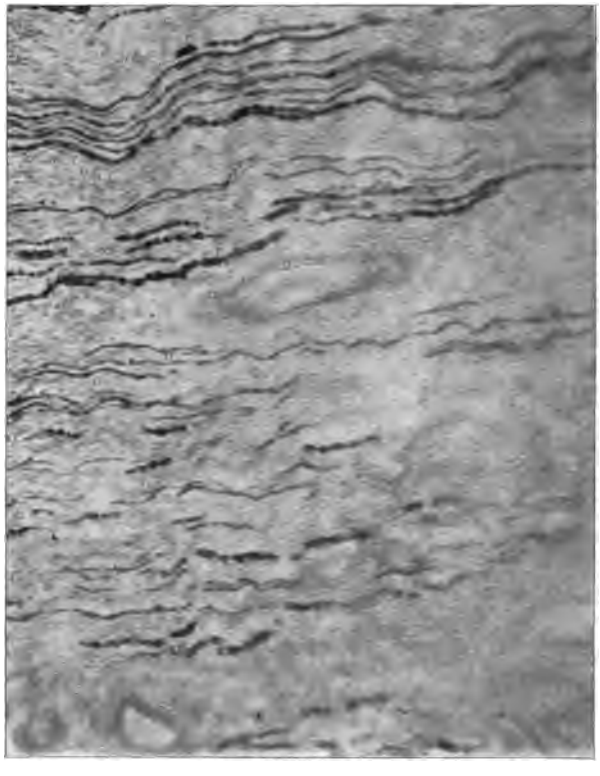
HISTOLOGICAL EXAMINATION. The various tissues were fixed in 4 per cent. formalin, Zenker's fluid, Müller's fluid, and in alcohol. Some of the bones and joints of the fingers and of the metacarpus of the left hand were placed while fresh in a mixture containing 10 parts of nitric acid and 90 parts of formalin, some in concentrated aqueous solution of picric acid, and others were decalcified in 5 per cent. solution of nitric acid in alcohol after hardening. Preparations from specimens decalcified in the formalin and nitric acid mixture, which acts rapidly and safely, show the histological structure very well indeed.

Frozen sections of the lungs show some emphysema, the lumen of the bronchi is filled with round cells and inflammatory exudate, and there is some infiltration in the surrounding air cells. In the liver there is slight infiltration in Glisson's capsule. The adrenals seem quite normal. The ovaries are normal; also the spleen and the kidney. The heart muscle has a visible cement substance, and the amount of pigment in the cells is increased. The abdominal lymph glands are normal; the inguinal lymph glands are vascular and cellular, but there are no necrotic foci.

The lining of the right frontal sinus is the seat of a marked round-cell infiltration; the covering cells show considerable mucous degeneration, and in places marked desquamation has taken place.

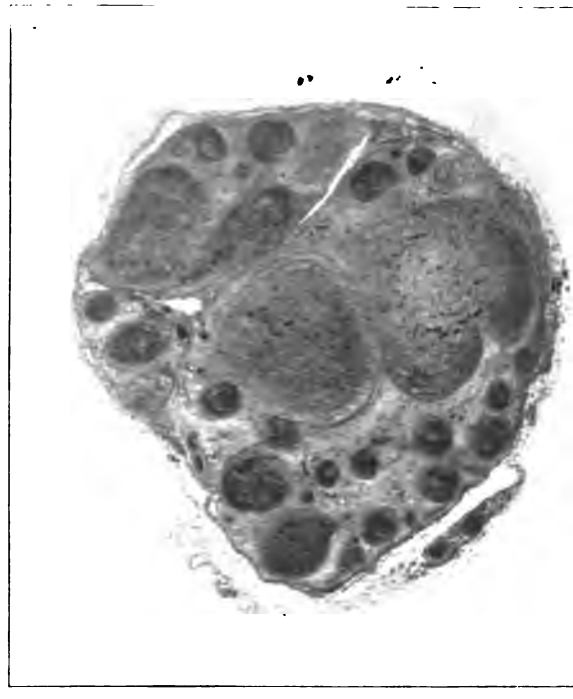
The yellow, irregular thickening of the serous coat of the small intestine is shown in microscopic section from embedded pieces to depend in part upon small cellular accumulations in the serous and subserous tissue and in part upon hyaline thickenings in the same places. These changes have taken place largely at the expense of the external muscular fibres, those immediately underneath the small hyaline areas being atrophic and encircled by bands of hyaline material. In the cellular areas the cells are endothelioid in appearance, having deeply stained nuclei and clear bodies; they are round or oval in outline. Small cell accumulations, as well as scattered cells of similar kind, also occur here and there between the muscular fibres, especially in the outer coat. In a few places the serous coat is strewn over

FIG. 5.



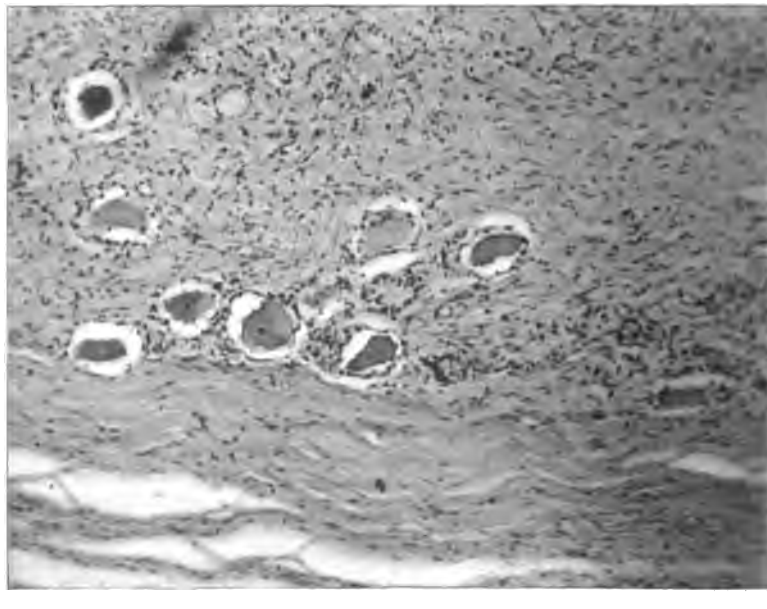
Degenerated nerves in fibroma of sciatic nerve. Weigert's stain. × 100.

FIG. 6.



Cross section of anterior tibial nerve. Nerves in central fibromata. Weigert's stain × 100.

FIG. 7.



Section of spinal ganglion involved in fibroma. Hematoxylin and eosin. × 150.

by a fine yellowish-brown granular pigment without any other changes being present. In some places in the small intestine the submucosa is congested and œdematous, the vascular spaces being widely dilated and the connective-tissue fibres spread apart by a finely granular or homogeneous eosin-staining material which contains some scattered leucocytes. The mucous membrane is partly absent; it is cellular, and contains in many places a fine granular brownish pigment. Sections stained for bacteria fail to show any. The distal end of the vermiform appendix is occluded, there being no mucous membrane present; in the proximal two-thirds the lumen is very small and filled with desquamated and mucoid cells; the muscular walls are much thickened, and in the subserous coat are small areas of more or less dense cell infiltration.

Paraffin sections of the thickened area in the skin of the leg show much increase in the depth of the corium, which is quite cellular and forms a few broad, variously shaped but mostly rounded papillary projections, covered by a quite normal epithelium, which is of varying thickness and again covered by an abnormally thick layer of horny material.

The Sympathetic and Peripheral Nerves. The following description is based on the study of sections of embedded specimens stained with hæmatoxylin and eosin, Von Gieson's method, and Weigert's method for demonstrating the medullary sheaths.

The majority of the nodules observed in the mesentery are fibromata connected with nerves, and not lymph glands; frequently a small lymph node and a fibroma occur side by side; other fibromata occur upon nerves in close proximity to vessels. The fibrous tumors appear to spring from the nerve sheaths. They consist of a typical, fibrillated, more or less cellular and more or less dense connective tissue. In most cases the fibrillar network is extremely tangled, but in some cases the fibres pursue quite parallel courses, bundles of parallel fibres crossing each other. The number of bloodvessels varies; in some places the tumors are quite vascular. The pigmented nodule in the pelvis appears to be an unusually vascular and cellular fibroma; in some places cells are especially numerous about small vessels; some quite large vessels have thin walls, and the tissue in which they occur is usually young. A few small recent hemorrhages are present; the nodule contains no ganglion cells.

Peripheral Nerves (Figs. 4, 5, 6). In some places the large fibrous mass in the thigh is somewhat œdematous. The sciatic nerve is the seat of large and small fibrous growths, circumscribed as well as quite diffuse, the fibrous tissue being distributed throughout nerve bundles, which then present the appearance of a marked proliferative interstitial neuritis. Many of the smaller nerve bundles with increased amount of connective tissue show an unusually large number of bloodvessels. Some of the arteries in the tissue between the nerve bundles show an almost complete obliteration of the lumen by intimal thickening. In the smaller bundles appear small vessels, whose lumen is wholly filled with nucleated cells.

Sections from the skin show many smaller and larger subcutaneous fibromata. The perineurium of the nerves of the skin is quite generally thickened and cellular, and there is evident increase in the fibrous tissue in the interior of the nerves not the seat of circumscribed tumors (Fig. 4).

Longitudinal sections of the sciatic nerves, stained by Weigert's medullary sheath method, show many intact nerve bundles and also many scattered and single, more or less degenerated nerves coursing through the intraneural fibrous nodules (Fig. 5). In some of the diffusely thickened nerves there may be but a few healthy fibres; in others the fibres are quite numerous, partly healthy, partly degenerated, and spread apart by bands and areas of fibrous tissue.

Cross-sections of the anterior tibial as well as of other nerves, stained in the same way, show also some healthy fibres in circumscribed, often central, tumor nodules, arranged around which are nerve bundles, in some of which are markedly degenerated districts (Fig. 6).

Many tumors give in the sections a quite decided reaction with Weigert's stain for elastic fibres, but accurate study of the distribution and amount of elastic tissue has not been made.

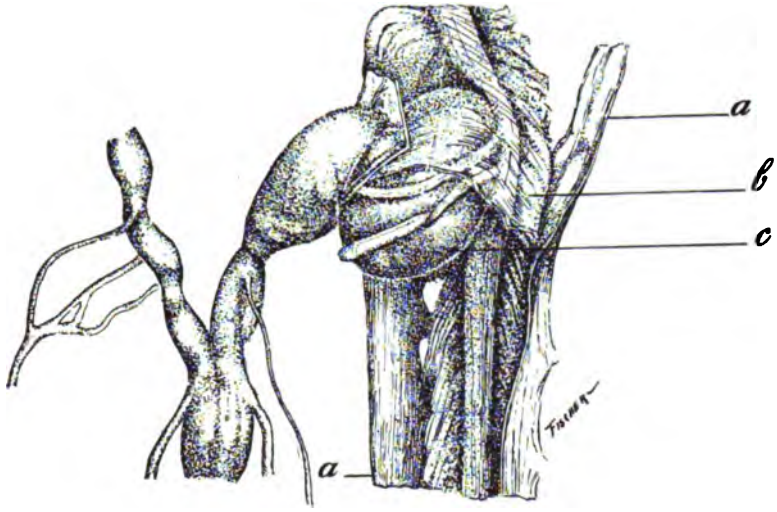
In none of the tumors were there any evidences of development of sarcoma.

Sections from the central part of the tumor corresponding to the fourth right cervical spinal ganglion shows a diffuse fibromatous proliferation of the ganglion, the ganglion cells are pressed far apart by the fibrous tissue, and occur singly and in small groups (Figs. 7 and 8). The ganglion cells show more or less shrinking of the body, occasional vacuoles in the protoplasm, and apparently the capsules are rather more cellular than in some of the healthy ganglions examined. When the ganglion cells occur singly they generally have an oblong and narrow form, and lie parallel with the bundles or strands of fibrous tissue. A few ganglion cells have been reduced to shapeless remnants without nuclei.

The hardened brain, when cut into thin transverse and longitudinal slices, shows only normal appearances.

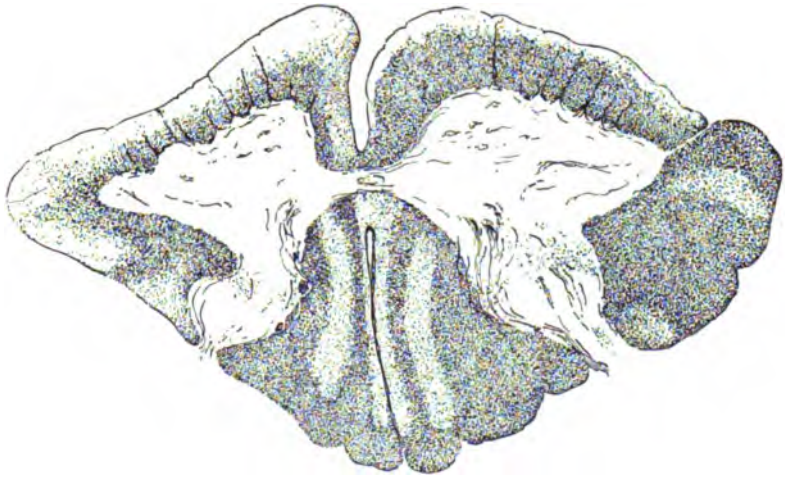
Examination of the formalin-hardened spinal cord shows that the gross changes due to the compression extend over a distance of 3½ cm. where the cord is greatly flattened (Fig. 8). The cord is thinnest in the centre of this part, and here it measures 1 cm. in breadth and 2 to 3 mm. in thickness. It has a concavo-convex appearance, the margins of the compressed part being the thinnest. The pia-arachnoid cannot be readily loosened from the surface of the flattened portion, which seems firmer than the cord ordinarily is. At the greatest change the cut surface does not present any recognizable normal outline. As one approaches the limits of the compressed part, it can be readily seen that the compression has been applied first upon the postero-lateral aspect of the left half, resulting in the disturbance first of the right posterior horn and posterior columns, and these are the parts which lie immediately subjacent to the subdural fibromata (Fig. 10).

FIG. 8.



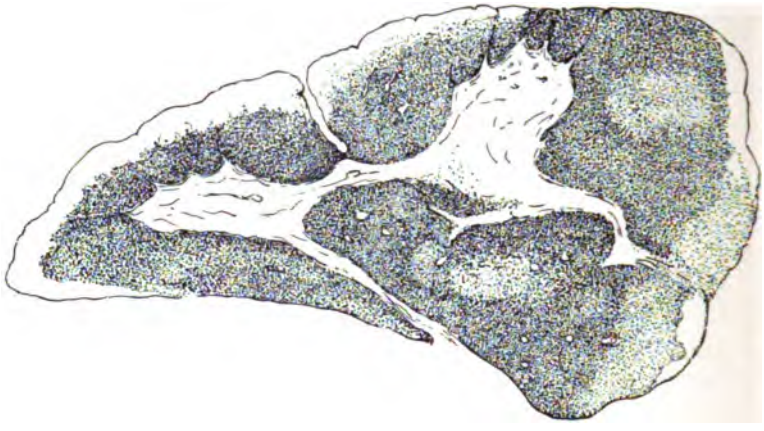
Compression of cord by intraspinal fibroma of fourth right cervical nerve. *a*, dura; *b*, pia, with compressed cord underneath; *c*, fibroma of the nerve. (Drawn from behind.)

FIG. 9.



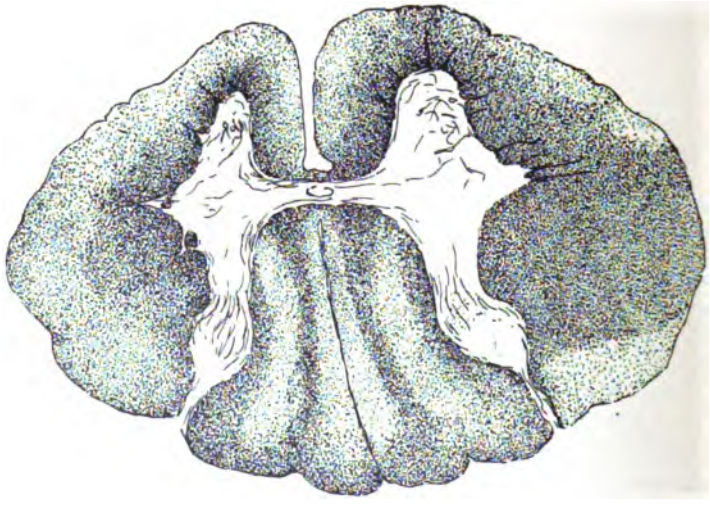
Section of cord above the tumor. Weigert's method. (For description of degenerated areas see text.)

FIG. 10.



Section of cord opposite tumor. For detailed description, see text. The section shows the deformity of the cord. Weigert's stain.

FIG. 11.



Section of cord opposite dorsal vertebra. For detailed description see text. Weigert's method.

There are no cavities in the compressed part, and the central canal is not dilated.

The changes in the cord and medulla were studied by Mr. Martin H. Fischer, with the following result:

Section through Middle of Medulla (Weigert's stain).

Distinct degenerative changes exist in the funiculus gracilis and the funiculus cuneatus. The restiform bodies show large numbers of degenerated fibres. The anterior pyramids show a general lightening. The evidences of degeneration are most marked in the central and peripheral portions of these tracts.

Section at Junction of Medulla and Spinal Cord.

The column of Goll is represented by a triangular lightened area lying close against the posterior median fissure. The apex rests against the gray commissure. At the periphery of this degenerated tract scarcely any nerve fibres can be found. The peripheral portion of the column of Burdach has suffered more severely, the most central part having suffered but little. The direct cerebellar, the lateral descending and ascending and the direct pyramidal tracts show severe grades of degeneration. The process is most marked in the peripheral portions of the cord. The decussating fibres of the pyramids seen at this level are well stained in Weigert preparations, though some degenerative changes can be seen.

The areas of degeneration are, in the main, symmetrical; still, those of the left half of the cord are of a severer type than those of the right.

Section Above the Tumor, Opposite the Fourth Cervical Vertebra (Fig. 9).

The entire left side of the cord has undergone a diminution in size. The columns of Goll and Burdach each show well-defined tracts of degeneration. The direct cerebellar, the crossed pyramidal, the antero-lateral ascending and descending, and the direct pyramidal tracts of the left side show scarcely any healthy nerve fibres. The crossed pyramidal tract of the same side shows a general lightening. On the right side a light rim of total degeneration marks the direct pyramidal and the antero-lateral ascending and descending cerebellar tracts. The entire anterior column of this side seems to have suffered a contraction. The tract of Lissauer shows a fairly well-marked degeneration on the left, but only a slight lightening on the right side.

The anterior and posterior horns of the left side show a diminution in size.

Section Opposite the Tumor (Fig. 10).

A compression of the cord substance has occurred to the right and forward. The compression involves the left lateral and posterior and the right posterior columns. The posterior median fissure has been obliterated. A

homogeneous unstained rim marks the position of the direct cerebellar, antero-lateral ascending and descending, and direct pyramidal tracts on the left side. The crossed pyramidal tract has suffered partial obliteration, and is perhaps represented by a lightened area of fibres at the posterior portion of the anterior horn. A marked degeneration is also noted in the direct pyramidal tract of the right side, with a questionable lightening of the crossed pyramidal tract. A narrow, well-defined area of degeneration is noted in the direct cerebellar tract of this same side. The two posterior columns have been fused into one through the obliteration of the median fissure. In the central portion of this is seen an area of lightening, as also just internal to the apex of the right posterior horn, which may correspond to the degenerations observed above in the columns of Goll and Burdach. The left anterior horn is markedly decreased in size. It is flattened antero-posteriorly, and the posterior horn proceeds from it backward and inward as a narrow unstained hand.

Section Below the Tumor, Opposite the Third Dorsal Vertebra (Fig. 11).

The columns of Goll and Burdach show a general lightening. A well-marked lightening has also occurred in the left lateral column of the cord, involving the crossed pyramidal, the direct cerebellar, and the antero-lateral ascending and descending tracts. The crossed pyramidal tract is involved only in its external portion. In the anterior columns the direct pyramidal tracts show marked lightening on both sides of the cord. The antero-lateral ground substance on both sides shows no change. A slight lightening has occurred in the antero-lateral ascending and descending tracts of the right side. Just external to the apex of the posterior horns small areas of degeneration are seen which correspond to the tracts of Lissauer. The anterior horn of the tumor side shows a diminution in size, having lost the rounded form possessed by the horn of the other side and assumed a more pyramidal shape. The posterior horns are also thinner than on the right side.

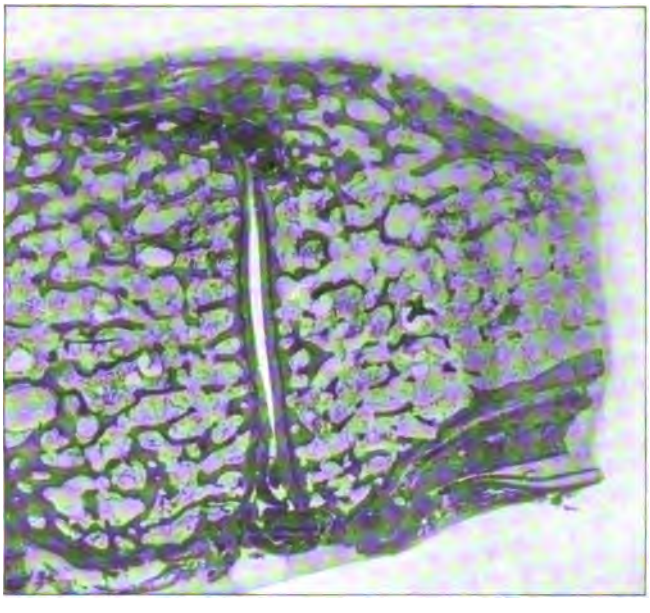
Section from Midlumbar Region.

The areas of degeneration correspond in the main to those described in the sections from the middorsal region. A larger number of healthy fibres are found just around the gray matter in the antero-lateral ground bundle on both sides. The degenerated tracts lie more at the periphery of the cord, and are rather indistinctly differentiated from each other.

The nerve fibres in the various localities show varying degrees of degeneration; many of the fibres are shrunken; others are much swollen, have lost their rounded form and become more or less oval and elliptical in shape. As a rule, the areas which show the greatest number of small, contracted fibres show the greatest increase in connective tissue (Van Gieson's stain).

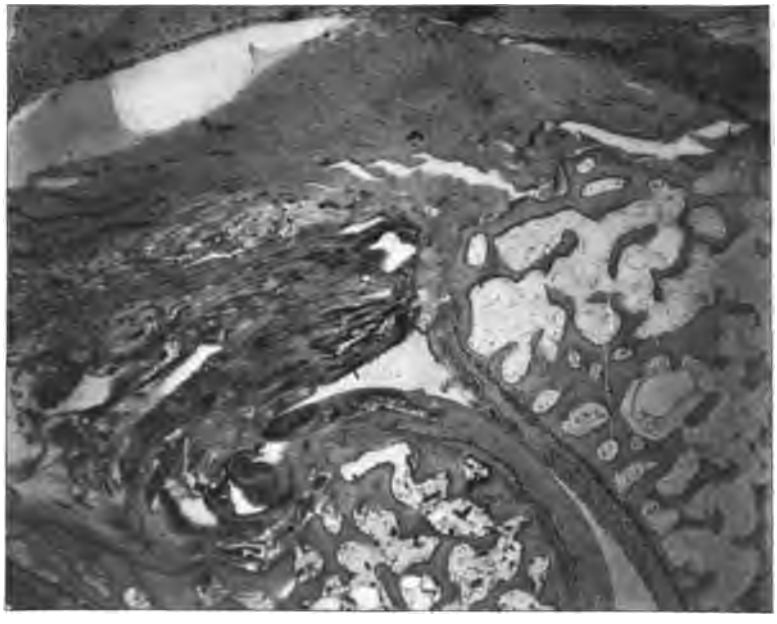
The myelin sheaths of the swollen fibres stain palely with Weigert's method. The neuraxons are more or less eccentrically located; in some

FIG. 12.



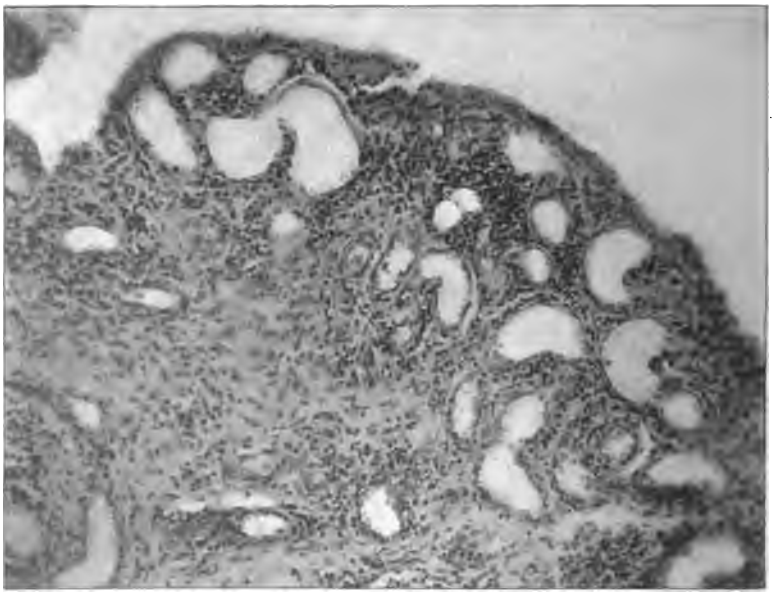
Section through a metacarpo-phalangeal joint of the left hand; shows the excavations at the margins of the articular cartilages filled with cellular connective tissue. The bone is porotic. Note the distinct junction between the cartilage and the bone. × 75.

FIG. 13.



Part of Fig. 12, more highly magnified. Note replacement of cartilage at the margin by cellular connective tissue, which is creeping over articular surface. See also wavy line at junction of bone and cartilage. × 200.

FIG. 14.



Section of villous outgrowth of synovial membrane, showing the cellular and vascular structure. × 200.

localities the neuraxons have been entirely lost, and only drops of myelin are left to represent nerve fibres.

The rule that the localities which show the greatest number of small fibres show the largest amount of connective tissue increase is not an absolute one, as the anterior and lateral columns of the cord on the left side just opposite the tumor show a great number of swollen nerve fibres. It would seem from this that as the tumor grew the increasing pressure upon the cord caused more and more fibres to degenerate, so that we have fibres in all portions of the cord in all stages of degeneration.

Marchi's method show but few black-stained fibres; these are seen most numerously in the peripheral regions below the seat of the compression, and more especially in the posterior portions of the cord. This reaction would go to indicate that while the majority of the nerve fibres represent old stages of degeneration demonstrable by Weigert's method, others are of more recent date, and so give the Marchi reaction.

Joints, Bones, Bone-marrow. The marrow of the femur is quite congested and there is considerable focal-cell accumulations. Among the cells are recognized (hæmatoxylin and eosin) quite a number of richly granular eosinophiles with small round nuclei, occasional megakaryocytes, and the ordinary narrow cells.

The joints of the left hands were the ones principally studied (Figs. 12, 13, and 14). The surfaces of the articular cartilages may be somewhat uneven, and just below it is a strip the matrix of which is a little fibrillated and split up, the cartilage cells being largely absent. The matrix of the principal part of the cartilage is quite normal, but there is usually more or less proliferation of the cartilage cells, leading at times to the accumulation of from four to eight or twelve cells in one capsule; the cartilaginous matrix is, moreover, rather granular and somewhat split up. In all cases the deeper layers of the cartilages are of a peculiar finely granular appearance and light bluish color (hæmatoxylin); this zone is of a wavy outline (Figs. 12 and 13); at the margin of the more healthy cartilage there is a deeper blue color, as if a cloud of blue dust granules had been swept up to this point. The cartilage cells in this zone are largely absent or the nuclei fail to stain, so that the capsules appear empty; in some instances the capsular space contains a few small chromatin particles. This zone is sharply demarcated from the underlying bone. At the peripheral margins of the articular cartilages a vascular and cellular fibrous tissue more or less directly connected with the synovial fringes has replaced part of the cartilage and fills the excavation which has formed in the bone proper at these points, extending sometimes for some little distance into the subchondral medullary spaces as well as creeping along over the articular surface of the cartilage, which now presents an escalloped appearance (Figs. 12 and 13). Generally the line of junction between the cartilage and fibrous tissue is sharp and abrupt, but islands of connective tissue occasionally appear in the interior of the cartilage as if formed by metaplasia, the matrix of the cartilage becoming fibrillated and

the cells liberated from the lacunæ, assuming the rôle of cells in fibrous tissue. The absorption of the bone has occurred principally at the margins of the articular cartilages, which often form overhanging shelvings over the fibrous tissue. There are no osteoclasts seen at the margins of the erosions in the bone. The medullary tissue is principally fatty; occasionally small focal cell-accumulations occur. At times medullary tissue has formed in the deeper layers of the cartilages. The synovial membrane where it turns over the articular cartilage is the seat of delicate and branching villous outgrowths which contain very many rather large arteries and other vessels, the stroma between being richly infiltrated with small round and oval nuclei, the whole presenting an appearance not unlike an angioma (Fig. 14). At other times the cells are larger, younger, and the vessels provided with thinner walls, so that the tissue looks like a recent granulation tissue. At some distance away from the joints there is more or less well-marked periosteal proliferation in the form of osteoid tissue.[1]

General Considerations (Dr. Preble). The case is an extreme degree of a very common condition, that of generalized neurofibromatosis, but has more than ordinary interest because it presents certain features which are rare, if not unique—the joint changes and the trophic changes in the skin.

Cases of fibrous tumors growing from the fibrous portions of the peripheral nerves have been recorded in medical literature since 1793, when Tilesius (quoted by Modrzejewski) reported the first case. No correct appreciation of their true nature, however, was suggested until 1847, when Brüch suggested that these tumors were due to polypoid growth of the neurilemma. Rokitansky shared this opinion. In 1880 Prudden collected forty-one examples of this condition. In 1882 Recklinghausen, by careful study of cases, showed that the fibroid tumors of the skin, the fibroma molluscum of Virchow, arose from the fibrous portions of the peripheral nerves. Since then these cases have attracted much interest and study, so that to-day there is a vast literature and a great number of cases recorded. When to the cases frankly of this nature we add the cases of conditions probably exactly similar, so far as their pathology and pathogenesis are concerned, though different in their clinical manifestations, the number becomes very large indeed. We should include many cases of elephantiasis, many cases of pigmented and linear nævi. The number

[1] These interesting changes in the bones and joints are reserved for a more complete consideration in the future.

could be easily still further increased, for lesser degrees of this condition of neurofibromatosis are so common that one could easily collect hundreds of examples in a few weeks.

Etiology. A very large number of the cases are congenital, but one cannot agree with Bruns, who says they are always congenital. There are many examples in which the first tumor has appeared some years after birth, as is illustrated by the case recorded above and by those of Generisch, in which the tumor appeared at eight, Lahman at twenty-three, Berggrün at ten, Hitchcock at nineteen, and many others.

In some cases, while no tumors are present at birth, there are congenital pigment flecks, and later the tumors appear. The case of Feindel and Oppenheim is an example of this, as is also the case of Spillmann and Etienne.

Not only are many of the tumors congenital, but in many cases they are found in other members of the same family: Herczel, mother and grandfather; Virchow, grandfather, father, and brother; Hecker, grandmother and parent; Czerny, grandfather, greatuncle, uncle, and mother; Bruns, two brothers; Hitchcock, mother and two sisters. Many other examples might be quoted, but no instance of extension through more than three generations has been found.

Some authors (Landowski and Feindel) believe, when the tumors appear late in life, that some exciting cause, such as bad hygienic surroundings, overwork, cold, trauma, or infection has been at work upon one who has a congenital predisposition to these tumors, and the tumors have resulted. The first case of Spillmann and Etienne may be an example of this. This patient, a male adult, had had pigment spots on the skin for many years, when, after a fall which stretched the sciatic nerve, tumors appeared scattered over the skin. Most authors believe, with Feindel, that there is during the development of the embryo some disturbance of the tissues derived from the ectoderm. If the disturbance is marked the effects in the way of skin tumors, tumors of the nerves and pigmented areas appear at birth. If the disturbance is less there is no sign at birth, and only later, under the influence of some incidental cause, do the results appear.

Recklinghausen, Etienne and others have suggested that the linear nævi which show such manifest relations to the peripheral nerve are due to an intra-uterine neuritis or myelitis, which so lessens the con-

trol of the nutrition of the skin that certain elements hypertrophy. Such fœtal neuritis might be due to some infection or intoxication from the mother. These linear nævi are seen frequently with skin and nerve fibromata, and it seems likely that they are due to the same underlying processes.

Other authors, notably Esmarch and Kulenkampf, suggest that there is a fibroid diathesis which is the cause of the neurofibromatosis; others suggest that it may be an intoxication like Addison's disease or myxœdema. Still others suggest a specific infection, which, like lepra, causes pigmentation of the skin, tumors of the nerves and skin.

Symptomatology. Following the example of Landowski, Feindel and Oppenheim, Briquet and others, we can conveniently divide the symptoms into four groups: tumors of the skin, tumors of the nerves, pigmentation of the skin, and functional disturbances. A completely developed case shows symptoms from all four groups; but there is a much larger number of cases which are incomplete, showing symptoms from three, two, or even one group only. The case reported above showed no areas of pigmentation, but symptoms from each of the other groups were present. The two groups most frequently absent from the clinical picture of the cases reported are the pigmentations and functional disturbances. I am inclined, however, to believe that note of the pigmentation is frequently omitted from the history sheets because of their apparent insignificance. If one takes into consideration the very numerous, incompletely developed cases seen almost daily in the clinic, one must conclude that the two symptoms commonly present are skin tumors and pigmentation, while the tumors of the nerves, and especially functional disturbances, are the exceptions.

Skin Tumors. The number of tumors varies from one or two to many thousands. In the case reported above there were many hundreds of tumors in the skin, scattered irregularly over the body. Modrzejewski reports one case with 3000 tumors. Virchow, in his book on tumors, has a picture of a patient who must have had thousands of these tumors. Lesser, in his text-book upon diseases of the skin, figures a patient who presents many hundreds of the ordinary forms of the fibroma of skin and nerves, and also the larger form, the molluscum fibrosum, ranken-neurom, or elephantiasis neuromatodes.

The tumors vary in size from that of a pin-head to that of a large egg. They may be sessile or pedunculated, tending to become the latter as they increase in size. The skin covering them may be perfectly normal, but with many of the tumors the skin is thin, relaxed, and thrown into fine irregular folds, looking as if it had been stretched for some time and then relaxed. Ordinarily the skin covering these tumors contains less than the normal amount of pigment, but it may be pigmented. Sometimes the skin grows large comedones; but these cases, as will be shown later, are probably not neurofibromata. The tumors are usually soft, but may be hard and dense. They are usually neither tender nor painful. They cause no disturbance except mechanically from their site or size.

In addition to these tumors, which are the common form, there are others of exactly the same nature, described under various names: fibroma molluscum, ranken-neurom, and elephantiasis neuromatodes. The resulting tumors are often very large, and may take the shape of fairly circumscribed tumors or of irregular thick folds, and laps of skin, such as are seen in the other forms of elephantiasis. The skin covering these folds may be unaltered until the mass becomes very large, when it tends to become inflamed. The skin is much more frequently pigmented than with the ordinary fibromata, and in some cases may be covered by growth of hair. The ranken-neurom is often seen in combination with the ordinary tumors, as is illustrated by the cases shown by Lesser, Herczel, Czerny, Kriege, Bruns and others, but may occur without them, but with pigmentation, as reported by Bruns; or we may find skin tumors, nerve tumors, and ranken-neurom combined in the same patient, as reported by Kriege.

These large tumors cause no disturbance except such as results mechanically, and cannot be distinguished clinically from other forms of elephantiasis except by the presence of the commoner manifestation of generalized neurofibromatosis.

Nerve Tumors. These may occur alone—*i. e.*, without skin tumors—as is illustrated by the cases of Lahman, Kriege, Keen, Spiller and others; but, as a rule, when multiple nerves are involved there are tumors of the skin also. Picque collected fifty cases of plexiform neuromas, in eighteen of which it is stated that there were cutaneous neurofibromata. The relative importance of the nerve and skin tumors varies in the individual cases. For example, in the case above

the tumors of the nerves are much more numerous and important. This is also true in the very extreme case reported by Berggrün.

The tumors vary in size from those which are too small to be palpated to the size of the large tumor in the right thigh—12 by 3.5 centimetres, or even larger. The tumors are round, oval, or fusiform, not attached to the surrounding parts, so that motion from side to side is permitted, but longitudinal motion in either direction is prevented by the want of elasticity of the nerve. Usually there is more than one tumor on a nerve, thus presenting an arrangement like a string of beads. The tumors may develop along the trunk of a nerve or along its branches. When the latter is true irregular convoluted masses result, which feel not unlike a varicocele, except for their density. The tumors, as a rule, are firm, but in some cases they are cystic. They are usually neither tender nor painful, but may be. The patient reported above had one tumor in the left side of the neck, which was tender and painful, although post-mortem it differed in no way from the other tumors found.

The tumors may affect a few nerves, or many, and there is no nerve in the body which may not be affected. The spinal, cranial, and sympathetic nerves are all found involved in many cases. As a rule, the involvement of the spinal and cranial nerves does not extend into the cranial cavity, but there are numerous exceptions. For example, the cases of Generisch and Berggrün, in which both cranial and spinal nerves were enlarged into the cranial and spinal cavities, and in the case of Czerny and the one above in which the enlargement of the spinal nerves extended within the dura, but the cranial nerves within the cavity escaped.

Pigmentation occurs in a variety of forms, colors, and arrangements. In many cases the only portions of the skin which are pigmented are those covering the tumors. In others the pigment occurs as flat or but slightly elevated areas, varying in size from that of a pin-head to a large plaque. The pigment flecks are usually most numerous over the covered part, the trunks, thighs, and arms, while the face, arms, and legs usually escape. Generally there is no sign of an arrangement of the pigmented areas, but in the case reported by Dupin and Dieulafe many of the pigmented areas were elliptical in shape, with a tendency for the long axis of the ellipse to lie parallel to the long axis of the limb. Feindel and Oppenheim note in their

second case that some of the pigmented areas follow the course of the nerves.

The color of these areas varies from light brown, café au lait, to dark brown. Usually there are no hairs in the pigment flecks, but in some cases, as in those of Marie and Bernard, Delore and Bonne, they are found. Briquet includes hairy and vascular nævi in his list of symptoms of this condition. In a case reported by Depaul and Verneuil, a tumor of neck near the scalp was covered by thick, coarse hair, which differed from that covering the scalp. Below this tumor were, under thick brownish skin, corresponding exactly to the distribution of the cervical plexus, nodular strings like a varicocele.

Functional Disturbances. One might expect that the tumors of the nerve would cause marked disturbances in their functions; but, as a matter of fact, even slight disturbances are rare. The commonest symptom in this group is pain, which may be spontaneous or appear on pressure. The pain may be in the tumor, or radiate to the area supplied by the nerve affected. Actual disturbances of function are less common, and may be sensory or motor, and be either of the nature of excitation or paralysis. Paræsthesia, hyperæsthesia, anæsthesia, cramps, tonic convulsions, weakness, and paralysis all are seen. A small number of cases suffer from arthralgia. In a few cases symptoms from involvement of the vagus have been seen; dysphagia, hoarseness, dyspnœa, palpitation, and tachycardia (Generisch).

Briquet saw vomiting and cramps in the abdomen in one case.

The case reported by Berggrün shows more marked disturbances than any case recorded, but in his case the enlargements on the cranial nerves extended to the cranial cavity, and many of the symptoms, such as paralysis of various of the motor nerves of the eyes and the optic neuritis were due to the intracranial tumors rather than to the fibromatosis of the nerves. Those few cases in which there has been paralysis of the bladder and rectum, atrophy of certain muscles, were probably cases in which the cord was compressed by tumors in the spinal canal. Extension into the spinal canal does not always cause symptoms, even when there is considerable pressure of the cord, as is illustrated by the cases of Generisch and Czerny and the case above.

Many of the patients are of a low order of intelligence, apathetic, languid, and stupid; but this is scarcely the rule, as some of the French authors consider it to be.

No descriptions of trophic disturbances have been found in any of the reports; there is, indeed, no mention made of them except by Landowski, who says they are very rare, and von Büngner, who says they are usually absent.

The patient, J. S., had for some years on the posterior aspect of one thigh an ulcer which looked in all ways like the perforating ulcers so often seen on the feet of tabetic patients, and resisted treatment in the same way. This was looked upon clinically as a perforating ulcer of trophic origin. The gangrene of one foot coming on spontaneously was regarded as of the same nature.

The joint changes in this patient might also be regarded as due to nerve influence. Their painless course and the great resultant deformity, together with the symmetry of the involvement in a patient whose peripheral nerves were so greatly altered, naturally suggested this idea. The distribution, deformity, and involvement of the spine were such as are seen in well-marked cases of arthritis deformans. In reviewing the literature no mention of joint changes was found except in the report by Berggrün and that by Dupin and Dieulafe. In Berggrün's case both hips and knees were strongly flexed, but could be moved passively, although the amount of motion in the hips was slight. The ends of the right femur and tibia were markedly thickened. At the autopsy the head of the left femur was out of the socket, the teres ligament was relaxed, the joint cavity was small and filled with loose, red tissue, and the head of the femur was flattened. Dupin's and Dieulafe's case suffered from rhachitis and repeated attacks of acute articular rheumatism when young, and the bone and joint changes may easily be the results of the early illnesses. The lower epiphyses of the forearms are enlarged, the first phalanges are flexed on the metacarpal bones, the third phalanges are extended, the phalanges are subluxated because of the relaxation of the ligaments, dorsal scoliosis, and double genu valgum are the changes noted. These are the only recorded cases of joint changes in the course of neurofibromatosis, and inasmuch as the disease in its milder forms is very common, and not very rare even in its severe forms, I believe, we must give up the very fascinating idea that there is some intimate relation between the two conditions and regard the combination as merely accidental.

The course of the disease is slowly progressive, and only in the

severest cases causes trouble and danger. Rarely we find exceptions to this slow course, as is illustrated by the case of Berggrün, which died at the age of eleven, directly from the effects of the neurofibromatosis. Many of the cases die from some intercurrent disease; others develop a gradually increasing anæmia and cachexia, and die from exhaustion; still others die from the effects of the accidental location of some tumor; still others die from sarcomatous degeneration of the fibrous tumor. This last is by no means infrequent, so that numerous cases have been recorded. Garrè collects seventeen cases of sarcomatous degeneration. The cause of this change in the nature of the tumor is unknown, but in some cases it seems to have been some trauma.

The *prognosis* in the milder cases is good, but in the severer forms must be conservative because of the danger of a tumor developing at some spot where it can mechanically cause serious disturbances, and because any tumor may at any moment become malignant.

Diagnosis. This is usually easy because of the marked and peculiar nature of the symptoms. Lahman has drawn attention to the fact that multiple fibromata of the skin may arise from the fibrous tissue of other parts of the skin than the nerves, and proposes dividing these fibromata into four classes according as they arise from the fibrous tissue of the nerves, the vessels, the glands, or from several of these. The differentiation of these may require microscopical examination unless there are deeper tumors having the character, location, and arrangement of tumors of the nerves.

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SUBPECTORAL ABSCESS.

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I HAVE seen in quite recent years three cases of subpectoral abscess under the following circumstances. Although belonging within surgical lines, they presented such clinical features that it was thought well to have a general practitioner see them, hence my experience. A few of the symptoms are worth emphasizing, as well as the phenomena which made it my privilege to observe them:

CASE I.—A previously healthy man, aged about thirty-five years, was admitted to the wards of the Presbyterian Hospital, suffering from an abscess of the chest walls under the pectoral muscle. With the local symptoms, which were not unusual but characteristic, there were some rigors and intermitting fever. There was also some mild arthritis. The patient was desperately ill, and my colleague asked me to see him to determine whether ulcerative endocarditis prevailed or pyæmia had begun; in other words, whether the infection was limited, or whether other structures and the blood were involved. The surgeon was deterred by the heart murmur and the pyæmic symptoms to give an anæsthetic or shock the patient by an operative procedure, which would, he feared, be useless. I felt the heart murmur was due to anæmia and flabby dilatation, intensified by the febrile process. The operation afforded prompt relief.

The feature of prominence was the excess of general symptoms (fever, etc.) in proportion to the local phenomena. No cause for the abscess was determined.

CASE II. was also a patient in the Presbyterian Hospital, presenting the local signs of subpectoral abscess. He was a rather delicate man of twenty-two years of age, with high fever, sweats, rapid heart, and some embarrassed breathing. Inability to thoroughly explore the chest by physical examination led to the fear that the abscess was secondary to an empyema. I was asked to consider this question. Empyema was excluded, based upon the

negative evidence on examination of the lungs posteriorly and laterally. Surgical treatment brought about immediate relief.

Trauma was the primary etiological factor. Its resemblance to empyema was the feature in this diagnosis.

CASE III.—A farmer of five and twenty years, robust, while training a colt, requiring physical and psychical strain, was drenched by a passing storm. This was followed by an attack of bronchitis and by apparent rheumatism of the right pectoral and shoulder region. His family physician prescribed salicylates. There was no relief and no signs of local infection. At the end of fifty-six hours he had a chill, followed by high fever. The bronchitis continued; the chest pains, limited to the right upper anterior half, were severe, and sweats were alarming. The symptoms continued one week. After the first examination the chest surface was not exposed for further study. Examination with the ear and by percussion was negative, for soon the mass under the pectoral muscle prevented the transmission of sound. With the continuance of fever and sweats the patient lost flesh and strength rapidly. The blending of the symptoms of bronchitis and those of the infection led the attending physician and his colleague to make a diagnosis of acute tuberculosis. I was asked to see the case, to decide upon climatic treatment. Fortunately I could demonstrate the presence of a considerable mass under the pectoral muscle, and could exclude any signs of localizing tuberculosis. I could not with the data at my hand exclude acute general tuberculosis, although I was certain the grave general symptoms were due to the subpectoral infection. Twenty-four hours later Dr. John B. Deaver opened the abscess, the extent and apparent virulence of which surprised him. The patient promptly recovered. Cultures yielded the streptococcus. Trauma caused the subpectoral bruise, leading to infection.

Here, again, the severe septic symptoms, unfortunately, coincident with the attack of bronchitis, led to an error in diagnosis.

There are two brief varieties—acute or phlegmonous, and chronic or cold, abscesses. The literature contains many cases, especially of the latter.

ACUTE OR PHLEGMONOUS SUPPURATION.

ETIOLOGY. 1. Traumatism is probably the commonest cause (Cases 1, 16, and 17), such as blows over the pectoral muscle Excessive use of the muscle has been given as an occasional cause (Martin).

2. Next to traumatism extension of inflammation from some other point in the body, either by metastasis (Case 5) or by extension through the lymphatic channels (Cases 2, 6, 7, 9, 10, 21, and 22), as

in those cases of suppuration following infected wounds on the arm or inflammation of the breast.

Pleurisy, either suppurative or non-suppurative, recent or old, is frequently the cause (Cases 4 and 15).

3. Rarely the malady seems to be idiopathic (Cases 11, 12, 13, and 20).

4. Taking cold has been described as a cause (Martin).

PATHOLOGY. The condition often proves fatal, so there have been a number of autopsies reported, and the pathology of the condition has been quite thoroughly studied. Certain anatomical considerations may be reviewed that will throw light on the phenomena observed. On the deep surface of the pectoral muscle is a cellular area lying on the ribs and intercostal muscles separated from them in the upper and outer portion by the lesser pectoral muscle and the costo-coracoid membrane. To the outer side lies the axillary space separated from the subpectoral space by the axillary fascia. There has been described a bursa interposed between the deep surface of the greater pectoral muscle and the ribs. Beneath the parietal pleura is a cellular tissue rich in lymphatics. These lymphatics communicating with the lymphatics in the cellular tissue beneath the pectoral muscle are of great importance as explaining the transmission of infectious agents from the pleura to the pectoral muscles.

The abscess usually occupies the cellular tissue between the deep surface of the pectoralis major and the plane of the ribs and intercostal muscles. The pectoral fascia, investing, as it does, the pectoralis major, offers an almost impassable barrier to the extension of suppuration beyond the muscles. Cases have, however, been reported in which the pus travelled along the pectoralis minor and entered the axilla along with the great vessels and nerves (Cases 15 and 21). There is often found, together with the pectoral abscess, an intrathoracic abscess, either subpleural or intrapleural, the external and internal cavities communicating through small openings. A case of pectoral abscess opening into the anterior mediastinum has been reported (Case 16); or, as in some cases, presenting no communication whatever. The latter are to be explained by the distribution of the lymphatics already mentioned. The suppuration, as it has been said, is limited to the pectoral muscle, yet within these limits it may be either diffuse (Case 13) or circumscribed.

SYMPTOMS. An interval of several days frequently elapses between the infection or traumatism and the onset of symptoms, but the symptoms may rapidly follow the cause. The commonest early symptom is a vague tenderness somewhere in the muscle. This may precede the development of the tumor by as much as a week. Soon after this movements of the arm become painful. Hence in some instances the diagnosis of rheumatism. Then follow in most cases the general symptoms: Fever, chill, loss of appetite, coated tongue. Then the local signs appear. There may be either a well circumscribed tumor, or the whole pectoral region may project forward; the latter is usual. Pain and tenderness are usually well marked. The skin, at first normal in color and temperature, becomes red, hot, and later œdematous, especially along the lower border of the pectoralis major, although in the third of my list of cases no local signs were noted for one week. The infraclavicular fossa is effaced by the swelling and the axilla encroached upon. Palpation reveals fluctuation. At first, when the tumor is deep seated, fluctuation may not be detected; but when considerable pus has formed, and there is a tendency to point toward the inferior border of the pectoralis major, it can always be elicited. The following method given by Prieur will usually be found satisfactory: If it is the right side that is under examination, place the fingers of the left hand under the anterior fold of the axilla, the pulp of the fingers being forward, the right hand over the pectoral muscle. With the fingers in these positions alternate pressure is made, as is usual in looking for fluctuation. The axillary vein and lymphatics of the arm are pressed upon by the swelling, giving rise to œdema of the upper extremity.

Such external abscess follows interlobular empyema. In two instances in children the intimal pus had found its way to the surface in the third interspace, presenting a globular tumor.

If the abscess communicates with another inside the thorax, other symptoms are added which make the diagnosis somewhat difficult. There is apt to be, in addition to the foregoing symptoms, cough and dyspnœa, together with the physical signs of a mass within the thorax. The external abscess may be affected by respiratory movements. It becomes tense on inspiration, flaccid on expiration. There is an impulse on coughing.

The infection is at times of a pyæmic nature. The symptoms

rapidly become typhoid, and death follows. These symptoms were noteworthy in my cases, and led the local symptoms to be considered of minor importance in the case.

DIAGNOSIS. The authors have little to say concerning this. When the abscess is entirely extrathoracic, careful physical examination would exclude any intrathoracic trouble. When there is a communication with an abscess within the thorax the diagnosis becomes more difficult. It will be considered below, under the heading of Cold Abscesses. In the early stages of the acute abscess, when the only local sign is tenderness and the general symptoms have not developed, the condition might be mistaken for rheumatism or intercostal neuralgia. Case III. of my list was thought to be rheumatic at first. But the diagnosis could not long remain doubtful on account of the course of the process.

COLD ABSCESSES.

Chronic or cold abscess in the region of the pectoral muscle. Cold abscesses of the thoracic wall have attracted considerable attention from the profession during the last half-century. It has been the subject of numerous monographs.

ETIOLOGY. Since the pathology of tuberculosis has been understood the nature of these cold abscesses has been made clearer. They are usually, perhaps always, tuberculous. They originate either primarily in the muscle (Morestin) or secondary to some other tuberculous focus, such as osteitis of ribs, pleurisy, or tuberculous cavity in the lung. The tubercular diathesis is commonly present. Traumatism is frequently a determining cause.

SEATS. 1. Antero-superior part of the chest, particularly near the costosternal articulations.

2. Posteriorly near the angles of the ribs.

3. The lateral portions of the chest.

We will consider only those abscesses occurring in the neighborhood of the pectoral muscle. These, indeed, are the most frequent.

PATHOLOGY. It may be primary in muscle, being the first focus of infection within the individual, or more commonly it is secondary to tubercular foci, as already stated. The abscess frequently occupies the cellular tissue on the deep face of the pectoralis major, and may involve the muscle itself. It is in these chronic abscesses that com-

munications with intrathoracic collections of pus are most common. The primary abscess is usually intrathoracic, having its origin either in a tuberculous osteitis or periosteitis of the internal face of the ribs or in a subpleural collection.

Small abscesses in the subpleural tissue have attracted considerable attention, and are thoroughly studied in the monograph of Marmarian. They probably originate by transferrence of infectious material from the pleural cavity through the lymphatics to the subpleural tissue without suppurative inflammation of the channels through which they pass. These subpleural collections, having their origin either in the pleura or in the ribs, increase in size, burrow through the intercostal muscles, and infect the subpleural collection without actual extension of inflammation by continuity.

SYMPTOMS. Localized tenderness develops long before the abscess in most cases, although occasionally the trouble may not be noticed until the abscess is of a considerable size. There are no general symptoms except those of the tuberculous diathesis. Local symptoms are characteristic, and usually quite different from those of acute abscesses. At first the tumor appears, varying in size from that of a pigeon-egg to a small orange. It is firm, rounded, not adherent at first; the skin is free over it, not reddened or hot; fluctuation is indistinct at first. When the abscess communicates with an intrathoracic collection or arises from a carious rib, it is adherent to the deep structures; later fluctuation becomes distinct, especially at the centre, while the periphery of the mass remains firm and the skin is apt to become adherent. Eventually the abscess points. Its course is slow, lasting over a year or two.

DIAGNOSIS. Before the tumor appears the localized tenderness may suggest intercostal neuralgia. The latter may be differentiated by reference to the points of Valleix, which, of course, are tender in neuralgia, while the tenderness of cold abscess may be at any point. After the tumor has appeared, on account of its indolent character it may be mistaken for a hydatid cyst, syphilitic gumma, lipoma, or a sarcoma. It can be diagnosed from these tumor formations by reference to the points commonly given in surgical text-books. Yet, it must be confessed, the diagnosis is often difficult. It may be necessary to resort to exploratory punctures.

When the abscess communicates with an intrathoracic collection

(indicated by reducibility and changes in tension during respiratory movements), it becomes necessary to determine whether the pleural cavity or the lungs are involved. The difficulty lies in the fact that the subpleural abscess closely resembles the ordinary pleural abscess or empyema, especially when the latter is encysted. A free collection of pus within the pleura may be distinguished by its movability. In either case the history of an acute pleurisy might throw light on the diagnosis. Radat gives the differential diagnosis between subpectoral abscesses originating within the thorax and those having their origin without. In the case of the former there is a history of some illness, such as pleurisy or "suppurative pneumonia." The fluctuation appears as soon as the tumor appears. If there has been pleurisy the respiratory murmur is absent, and there is dulness on percussion. If the abscess has its origin within the lung there is dulness and bronchial breathing and other signs of "chronic pneumonia, such as moist râles, cavernous breathing, etc. The writer must emphasize the great value of the history indicating the sequence of pathological events, with the physical signs and the immediate occurrence of fluctuation.

The following cases are gathered from the literature to illustrate the statements made above:

Case 1 (Briband). Etiology. Blow on the right breast. Symptoms, painful swelling limited to the pectoralis major appeared soon after injury. There was immobility of the arm; skin was not involved; fluctuation just below the clavicle; œdema of the surface. Operation. Death in three weeks from sepsis. Autopsy. Abscess of the posterior surface of the muscle, limited by its aponeurosis; adherent pleura opposite the abscess; peritonitis.

Case 2 (Briband). Etiology. A man, aged forty-three years. Angioleucitis from furuncle on the arm, followed by enlargement of the axillary glands. Symptoms, abscess limited to the pectoral muscle, causing painful swelling of the whole region. Skin hot, red, and œdematous; arm useless. Fluctuation at inferior border of muscle. Operation. Recovery. Pathology. Operation revealed large cavity under the pectoral muscle containing bloody pus.

Case 3 (Briband). Etiology. A woman, aged thirty-five years. Followed a cured mammary abscess. Interval not stated. Symptoms: First, tenderness at the insertion of pectoralis major, then swelling of whole pectoral region. Redness of the skin; obscure fluctuation below; marked general symptoms. Operation. Recovery. Was diagnosed *rheumatism* at first.

Case 4 (Briband). Etiology. From an old pleurisy. Symptoms: Began with chill and other general symptoms, followed by swelling of the pectoral muscle. Terminated in death. Autopsy. Subpectoral abscess extending into the axilla. Two localized abscesses in the pleura in the pectoral region. An old pleurisy with two litres of fluid.

Case 5 (Renant). Etiology. An abscess at the elbow, of unknown origin. Two abscesses developed—one at the anterior fold of axilla and one opposite the middle of the sternum. Purulent cough followed; pressure over abscess produced gurgling; subcutaneous emphysema toward the clavicle. Terminated in death. Autopsy. Subpectoral abscess, involving muscle opening through the third interspace, through the pleura into the lung. No signs of tuberculosis in the lung. Pleura adherent only at the point of perforation.

Case 6 (Prieur). A young sailor, perfectly well, developed a swelling limited to the pectoral; freely movable; painful, indistinct fluctuation; skin red; no fever or other general symptoms. Diagnosed as *syphilitic myositis.* A deep incision through the pectoral gave vent to pus. Patient had an infected finger.

Case 7 (Prieur). A man, aged twenty-eight years. Blow on the finger caused inflammation, which recovered without treatment. Six days after developed pain in the axilla, fever, and anorexia. Pectoral muscle tender and swollen. Motions of the arm painful. Incision at lower border of the muscle opened a pectoral abscess.

Case 8 (Prieur). Man, aged sixty-two years. Anterior axillary wall swollen, tender, and hard. Faint fluctuation; subpectoral abscess opened by incision along lower border of muscle.

Case 9 (Lesigne, quoted by Prieur). An abrasion on finger, followed by pain in the pectoral muscle; then general symptoms. Great pain on motions of arms. Pectoral muscle then became swollen. Subpectoral abscess opened by incision. Case was diagnosed as *acute articular rheumatism* before abscess developed.

Case 10 (Lesigne, quoted by Prieur). Abrasion of finger. Angioleucitis extending up the arm, followed in six days by swelling of the axillary glands. Œdema and immobility of the arm. In twelve days pectoral abscess. Incision below pectoral muscle. Death.

Case 11 (Watson). A pulsating swelling below the clavicle, nothing in history to account for it. Pulsation ceased. Signs of pus increased. Abscess opened and ordinary pus was evacuated. Pulsation probably due to proximity to axillary or subclavian artery.

Case 12 (Frost). Patient was a pronounced alcoholic. Had been on a spree; was admitted to the hospital unconscious. The day before felt ill, and the right arm was stiff; examination showed pectoralis major prominent and œdematous along the lower border. Arm œdematous. No operation. Death in twenty-four hours. Autopsy showed diffuse suppuration under the pectoral muscle.

Case 13 (Martin). Case of subpectoral abscess from excessive use of the muscle.

Case 14 (Velpeau). Began with a chill and vague pains in the left side. The next day general symptoms developed. Pectoral muscle became tender, swollen, and indurated. Then œdema and fluctuation developed. Abscess opened along lower border of muscle. Symptoms were relieved. After two days the fever rose and pleural effusion appeared. The patient sank and died after nine days. Autopsy showed subpectoral abscess extending along the pectoralis minor into the axilla. The pleura contained two circumscribed abscesses about opposite the subpectoral abscess. Both had thick walls, and were evidently old. There was no communication between them and the external abscess. The pleura contained two litres of fluid; the lung was normal.

Case 15 (Allen, H.). Patient admitted to the hospital seriously ill. Weak pulse and rapid respiration. Examination showed the usual signs of subpectoral abscess, with one peculiar symptom—namely, appearance of a wave at the summit of the collection during expiration. Operation; death. Autopsy showed subpectoral abscess communicating with the anterior mediastinum through an ununited fracture in the third rib.

Case 16 (Scholz). Young man, aged twenty-three years, perfectly well, kicked in the right breast two months before admission. The pain of the injury disappeared, but was followed by a swelling extending from the sternum to the border of the pectoral, from the second to the fifth rib. Skin red, slightly higher in temperature. When the pectoral muscle was put in action, swelling became harder and the inner portion bulged forward. There was no pain, only tenderness on pressure. No general symptoms. Operation followed by erysipelas, pyæmia, and death. Autopsy showed caries of the fourth rib, subpectoral abscess, emboli of the lung, peritonitis.

The author reports a case from Pitha's clinic of traumatic subpectoral abscess due to shock of revolver. The infection extended to the abdominal cavity.

Case 17 (Cheever). A young man, possibly syphilitic, otherwise perfectly well, developed swelling in the region of the pectoral, partially obliterating the axilla, considerable pain, abscess pointed.

Case 18 (Cheever). Young unmarried woman. Abscess under the left pectoral, the left breast prominent, superficial veins engorged, the left axilla partly filled, general symptoms very great; operation, recovery. The author pointed out the great resemblance to mammary abscess and to subcutaneous emphysema.

Case 19 (Werner). Young girl, aged seventeen years, began with pain in the pectoral region and immobility of arm. Swelling followed at the border of sternum at level of third rib. Skin at first normal, later reddened, general condition good. Abscess opened, large subpectoral cavity found. Recovery.

Case 20 (Werner). Woman, aged thirty-three years. Sometime before

had a wound of the finger that healed perfectly. Eight days before observation, developed pain in the axilla, and infraclavicular region filled up, swelling of the pectoral region, general condition good. Axillary glands were irritated and enlarged; abscess opened, found to extend into the axilla.

Case 21 (Werner). Boy, aged fourteen years. Developed traumatic scarlet fever(?) from an infected wound of one finger. Then, after subsidence of rash, swelling developed in the pectoral region, which was opened, giving exit to yellow pus. Extensive cavity extending nearly to the clavicle. Recovery.

Case 22 (Werner). A man, aged thirty years, seized with severe pain in the left arm which extended to the pectoral region, was followed by development of an abscess. The pain in arm probably due to swelling of axillary gland. Operation; recovery.

Case 23 (Stiftung), illustrating communication of abscess with lung. Patient, aged forty-six years; day laborer. Had been suffering for eight days, without known cause, from an abscess under the left collar bone. The clavicular portion of the large breast muscle was gone. The left lung was tuberculous. On the tenth day afterward, in the morning, the abscess broke and the hand showed, on pressure, a knotted mass. The patient was breathing with difficulty. In the night he had a very severe coughing attack, mucous expectoration came freely, and the abscess broke into the lung. It contained air and fluid. Pressure with the finger would empty the abscess, and a full breath would fill it with air. The coughing continued very severely, excited by the pressure. The abscess grew smaller, and in fourteen days there was only a little hole and a little fluid. Communication with the thorax was almost closed up, and fourteen days after that there was no fluid discharged.

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REFRACTORY SUBCUTANEOUS ABSCESSES CAUSED BY SPOROTHRIX SCHENCKII. A NEW PATHOGENIC FUNGUS.

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(PLATES I. AND II.)

IN the *Bulletin of the Johns Hopkins Hospital* for December, 1898, there appeared an article by B. R. Schenck "On Refractory Subcutaneous Abscesses Caused by a Fungus Possibly Related to the Sporotricha." "The primary point of infection was on the index finger, whence it extended up the radial side of the arm, following the lymph channels, and giving rise to several circumscribed indurations, which were in part broken down and ulcerated." This infection proved very refractory to treatment. The organism supposed to cause the lesions in this case was obtained in three cultures from two different foci of the disease, twice in pure culture.

Schenck carefully describes the cultural characteristics, the morphology and development and the results of the inoculations of this organism, which Dr. Erwin F. Smith, of the United States Department of Agriculture at Washington tentatively assigns to the genus *Sporotrichum.*

During the last few months we have had occasion to study a case presenting similar refractory subcutaneous abscesses from which an organism has been isolated which is identical in the essential details with the one described by Schenck.

CLINICAL HISTORY (Dr. Perkins). On March 16, 1899, Charlie C., aged five years, was brought to my office by his parents, suffering with a sore upon his left index finger, concerning which I elicited the following history: Ten days before he had been using a hammer and had struck himself, denuding a surface as large as a split pea on the dorsal surface and over the second joint. This abrasion did not heal up as his father thought it should, and he applied some "verdigris salve" to the injury. At present the finger, from the first to the third joint, is swollen to twice its original size, presenting in the centre a deep, well-defined, sharp, undermined ulceration, the size of a ten-cent piece. The base of the operation is rough and covered with grayish-looking pus. This, when sponged away, leaves a bright-red surface; the ulcer extends through the whole thickness of the skin. Surrounding the ulcer over about one-half of the infiltrated area are a large number of vesicles and a few pustules. The dorsal surface of the hand and the extensor surface of the forearm present a chain of swollen lymphatics, along which are about twenty nodules the size of a small pea to a large hazelnut. There is no evidence of suppuration in any of them at this time. The little patient does not complain of much pain, either in the finger or arm. The hand is cleaned with green soap and washed with sublimate solution 1:2000, the surface of the ulceration mopped over with 95 per cent. carbolic acid, powdered boric acid dusted on, and bichloride gauze and borated cotton applied.

Subsequently the dressing was changed every second day for ten days and reapplied as at first. At the end of this time ulceration had increased to nearly twice its original size. The nodules are somewhat larger and are getting tender, though I cannot detect pus, either by fluctuation or aspiration. On March 28th I began using iodoform as a dressing, but met with no better results. Do what I would, I could not get the finger to improve in the least. The vesicles had formed pustules, and the epidermis over nearly all of the infiltrated areas had loosened, leaving a raw, oozing surface.

During the first ten days under my care the child seemed to feel reasonably well, but he now began to develop a little fever, and for the next month the temperature ranged up to 100.5° F. There developed, about April 1st, an annoying and persistent cough and coryza. Early in April the swollen lymphatics began to suppurate. I opened and curetted eleven abscesses in the next week. Some contained not more than thirty minims, others probably four drachms of pus. Upon opening one large abscess about the middle of the forearm I was surprised to see it drain another smaller one four inches from the incision. This was refilled with the irrigating solution and opened. The fistulous tract was irrigated and a swab with carbolic acid upon it was passed through. The pus from the abscesses was of a mahogany color, thick and tenacious.

Up to this time (May 25, 1899) I have opened twenty-one abscesses, four have opened spontaneously, and still there are more to follow.

The lymphatic glands in the axilla and neck on the left side have been

inflamed, but are smaller now, and bid fair to return to their normal size without suppurating. The abscesses which have been opened have shown considerable destruction of the fascia, intermuscular septa and skin.

Suspecting farcy and with the expectation of having my opinion confirmed, I inoculated two tubes with a quantity of pus from an uncontaminated abscess and mailed them, May 2d, to Prof. L. Hektoen for examination. At his request I again sent him tubes about May 9th or 10th.

The family being poor, I have had the mother dress the arm part of the time. I once saw her doing this when she had a cut over one-half inch long on the thumb. The quantity of pus from the sores was large at this particular time, and it seems impossible that she did not get germs into the wound. This fact and that the patient has mingled with several other children in the family have convinced me that the danger of infection is not very great.

Internal treatment has varied somewhat. Cough mixtures for two or three weeks; calcium sulphide in ¼-grain doses; corrosive sublimate 1/100 grain, with quinine sulphate 1 grain. The last named associated with wet dressings of 1 : 100 carbolic acid seemed to do the most good. Two small photographs were taken before any of the abscesses had been opened. A larger one was made May 25, 1899, which shows the present condition very well (Plate I., Fig. 1). The boy's condition has improved very materially, and my opinion is that he will fully recover in another month (which proved to be the case).

Bacterial Examination. The glycerin-agar tubes, inoculated by Dr. Perkins on May 2d and again on May 10th, all developed pure cultures of the organism in question. After about six days, the last four being in the incubator at 37° C., there appeared several grayish-white, raised, irregular colonies, about as large as a pinhead, confined exclusively to the area of the surface of the medium covered by the bloody exudate. In one tube similar but smaller growths appeared in a small quantity of exudate accidentally smeared upon the glass. The colonies were rather dense and viscid; considerable increase took place and wrinkled masses formed. Repeated subcultures upon various media show the following cultural characteristics:

Agar (Plate I., Figs. 2 to 4). At the end of twenty-four hours in the incubator there is some growth of a grayish color and granular in appearance along the streak on plain and glycerin agar. After forty-eight hours the growth appears as a delicate, slightly raised, whitish line with symmetrical feathery fringes and some hairy downgrowth into the substance of the agar. At the end of seventy-two hours the growth assumes the form of a band with numerous transverse wrinkles; in a couple of days more the surface becomes more markedly corrugated and looks like the chains of mountains on a map.

About the seventh day the growth, which has increased some in thickness, becomes light brownish in color, the margins being smooth and wavy, marked by shallow transverse grooves. Still later the growth becomes distinctly and even dark brown, the surface wrinkled and velvety, in some cases covered by a very delicate fuzz. The medium becomes slightly brownish.

On wort-agar a thick, yellowish, wrinkled membrane develops, extending some distance upon the sides of the tube. This, or glucose-agar, is one of the best media for rapid growth.

The individual colonies upon glycerin-agar plates appear at the end of two to four days as irregular, grayish-white dots, 0.4-1 mm. in diameter, resembling somewhat minute flakes of snow. Under the microscope they are made of a central network of threads which at the periphery grow outward in a radiating manner and become tipped with small clusters of minute dots; similar dots (conidia) also appear along the sides of the outgrowing threads (Plate II., Fig. 5).

Individual colonies on agar slants, after three or four days, appear as minute shreds which gradually develop into round, circumscribed, raised, somewhat pearly masses, which send fluffy prolongations into the medium; later the surface of the spreading colony becomes raised into irregular wrinkles and eventually a brownish color generally appears.

The early surface growth in the glucose-agar stab presents a whitish, heaped-up centre and delicate radiating margins; with time a uniform growth develops along the stab with fine, thickly-set lateral branches. No fermentation.

In one or two instances streak cultures upon the agar have resulted in a flat, granular, sparse growth only, consisting almost wholly of round and oblong budding bodies. Subcultures from such growth give rise to characteristic folded and wrinkled membranes.

Blood Serum. In forty-eight hours small colonies appear which are covered by a white frosting; the growth increases slowly but presents no special characteristics. There is no liquefaction.

Gelatin. The deep growth is confined to the upper end of the stab; it increases slowly and sends out lateral branches which are longest immediately underneath the surface, which becomes covered by a flat, spreading layer. At the end of about six to seven days a slight liquefaction is apparent; in about fourteen to eighteen days later the liquefaction is nearly complete, the surface is covered by a dense membrane which has a tendency to sink down into the clear liquid.

Wort-gelatin, acid gelatin, and 4 per cent. glycerin gelatin are more favorable for growth, and liquefaction takes place earlier; on shaking, the thick surface layer falls to the bottom, afterward a new layer forms on the surface, and delicate threads may be seen growing vertically along the space of the tube. The liquid gelatin remains clear.

Potato. Twenty-four-hour cultures show a slight brownish-gray or yellowish nodular growth which increases quite rapidly, becomes raised and wrin-

kled, the surface presenting smaller and larger districts of a white, frosted appearance. The older growths become discolored at the same time as the potato is darkened.

Milk. Litmus milk is not changed in color and not coagulated; but slight growth takes place.

Bouillon. The growth is fairly abundant; little tufts or shreddy masses form which settle at the bottom or cling to the sides of the tube; a white, crumbling surface-film is occasionally observed; no change in reaction. The rate of growth seems about equal in plain, glucose, and glycerin-bouillon.

Vegetable Infusions. The fungus grows in hay, turnip, carrot, and potato infusions as a whitish, flocculent precipitate, the fluid remaining clear.

Hydrant Water. A very slight growth?

Gasperini's Starch. A flat, slightly raised, grayish-white, hard layer forms rather slowly.

Fermentation Test. Glucose, lactose, and saccharose bouillon, prepared according to the method of Theobald Smith,[1] show a characteristic growth in the aërobic bulb, the anaërobic tube is unchanged and there is no gas formed.

Anaërobiosis. There is no growth in the tube in Buchner's jars.

Temperature. The optimum temperature for development would seem to be about 37° C.; good growth occurs at the room-temperature, but at a much slower rate. No growth occurs at a temperature just above the freezing-point, but cultures kept at this temperature for five weeks remain alive and give rise to vigorous new growths on reinoculation.

Thermal Death-point. The organism is killed by an exposure to 60° C. for four and a half minutes; a slight growth occurred after an exposure to this temperature for four minutes. No growth could be obtained after exposure to 59° for ten or five minutes, to 61° and 62° for two minutes, to 65° for one and a half minute.

MORPHOLOGY. Cover-slips from the cultures, stained with methylene-blue, show masses of more or less parallel, or tangled, straight or curved, unevenly stained, rather thick threads with rather infrequent true side branches. Interspersed among the threads lie numbers of ovate or apiculate bodies, from 3 to 5 μ in their longest diameter. In the stained preparations no definite connection is to be made out between the majority of the bodies and the threads. In some preparations the bodies predominate. Occasionally bodies are seen connected with a thread by a small pedicle. The threads seem thinner when stained with Gram's method, which gives them a light violet, granular appearance with irregular clear spaces. Gram's method stains the spore-like bodies a deep blue; occasionally there is an unstained area in their interior. Some spores appear to be growing out to form short threads.

In the unstained preparations and in hanging-drop cultures of bouillon and gelatin the threads of the mycelium are seen to be doubly contoured;

[1] Journal of Experimental Medicine, 1897, ii. p. 546.

the protoplasm is somewhat granular and interrupted at fairly regular intervals by transverse septa; the diameter of the threads varies somewhat, the average being about 2μ; the branches are not frequent and do not bear any fixed relations to the septa.

In the hanging-drop cultures the relations of the conidia to the mycelium are very nicely shown. The spore-bearing branches, which grow out in a radiating manner from the central felt-work, are commonly tipped by a cluster of from three to six or more conidia, which, in the case of the larger clusters, are attached by the smaller end to the slightly expanded extremity of the branch. Similar ovate buds also arise from the sides of the hyphæ at shorter or longer intervals.

The spores are also doubly contoured and granular, resembling very much yeast-cells.

These various features are well shown in the photographs of the growing hanging-drop cultures (Plate II., Figs. 6 and 7).

The attachment by means of short pedicles of the spores to the threads is very easily severed, as shown by the difficulty in obtaining stained preparations with the spores *in situ*.

Development. When placed in the hanging-drop the conidia grow out into one or more straight germ-tubes which spring from either or both ends or from the sides. These embryonal threads again give rise to lateral or terminal buds, which in all particulars resemble the spores, and some of which form branching spore-producing threads, so that in the early stages very peculiar-looking bodies are produced.

HISTOLOGICAL EXAMINATION. A small bit of skin, including part of the wall of an abscess, was excised by Dr. Perkins and sent to me in alcohol. The sections show some thickening of the epithelial layer: there are rather broad interpapillary downgrowths. On the cutaneous surface there is much horny material, altered red blood-globules, detritus and polymorphonuclear leucocytes often collected into dense foci within and upon the horny layer. The epithelium and the cutis show many leucocytes, with long drawn-out, thread-like and contorted nuclei, apparently going in various directions and also aggregated into small groups. The vessels of the cutis are congested.

Along one side and part of the lower or deep surface of the section there is considerable bloody and leucocytic exudate; the adjacent tissue is infiltrated with leucocytes with great elongated nuclei which might be taken for fragments of fungus threads.

In sections stained by the Weigert and Gram methods are short threads, which cannot be otherwise distinguished from the leucocytic nuclei mentioned. With this possible exception no micro-organisms are seen.

ANIMAL EXPERIMENTS. *Rabbits.* I–II. Injections of 2 c.c. of a twenty-four-hour bouillon culture into the abdominal cavity and into the ear vein of two large rabbits respectively produced no symptoms in eight weeks.

III. A few drops of a bouillon culture inserted into the anterior chambers of the eyes of a small rabbit in three days produced a moderate whitish

exudate, and a few, pin-head-sized, white clumps formed, which persisted for two days, after which rapid recovery took place.

Guinea-pigs. I–III. Intraperitoneal injections of 2 c.c. of a suspension in bouillon did not produce any symptoms or changes after six weeks in the case of three animals.

IV. May 17th I injected a guinea-pig with 2 c.c. into the subcutaneous tissue over the abdomen. A number of small, pea-sized, firm nodules developed about the site of the injection. The animal died May 29th. The subcutaneous nodules were small abscesses; in the pus were numerous oval and oblong bodies staining irregularly with methylene-blue and with Gram's method. No other organisms were found and pure growths of the sporothrix developed in the cultures from the pus. The internal organs were sterile and of normal histological structure.

V. A guinea-pig inoculated subcutaneously with 2 c.c. July 25th died August 18th. There were no local changes visible, and cultures from the internal organs remained sterile. At this time a number of guinea-pigs in the laboratory were dying from unknown causes.

Dogs. I. Intravenous injections of 1 c.c. of a suspension in bouillon did not produce any symptoms; all organs appeared to be normal and proved to be sterile when the animal was killed on the thirty-fourth day.

II. Two c.c. of a bouillon suspension were injected into the subcutaneous tissue of a large female dog. In a few days a small swelling appeared which was quite tender; a diffuse slightly tender induration remained for some time.

Twenty-eight days after the first injection 2 c.c. were again inoculated under the skin of the thigh, followed by the development of a small, fluctuating swelling. There was no enlargement of the corresponding inguinal glands. The animal was killed on the fifteenth day. The internal organs were normal and sterile. At the site of the first injection was an area of scar tissue which, on microscopic examination, showed islands of marked round-cell infiltration; no organisms could be demonstrated in the sections, and the cultures from the scar tissue remained sterile.

At the site of the second injection was a small, soft, whitish spot or cavity containing a gelatinous material, smears and cultures from which showed the organisms injected to be present in fair numbers. The sections, stained by Gram's method, showed organisms in fair numbers among the leucocytes in the little cavity, which was enclosed in a recent fibrous tissue. The organisms resembled somewhat the conidia of the fungus, stained irregularly, and varied in size, being oval or oblong, and from 2 to 3 or 4 μ in length.

III. Intraperitoneal injection of 2 c.c. of a bouillon suspension did not produce any lesions, the organs being healthy and sterile when the animal was killed on the twenty sixth day.

White Rats. I. Subcutaneous injection of 2 c.c. of a bouillon culture did not seem to have any effect, the animal remaining well and fat.

II. About two months after the intraperitoneal injection of 2 c.c. of a bouillon culture, during which time the animal remained well, it was noticed

that the scrotum was very large and dragged on the ground, interfering with the animal's movements; the hind legs were œdematous. Killed by chloroform. The larger part of the small intestine and omentum occupied the two sides of the scrotum. The peritoneum over the lower third of the abdominal cavity and lining the scrotal cavities was covered with numerous yellowish, tuberculiform nodules, arranged now singly, now in groups or clusters. On incision each nodule was found to contain a quantity of yellowish-gray, viscid, purulent material composed of leucocytes and innumerable, irregularly stained (Gram), oblong and oval conidia from 2 to 4 μ in length. Many presented a transversely striated appearance; in others there was a clear spot near one end. There were no threads present in the pus. The other organs seemed normal; cultures from them and from the heart's blood remained sterile: no organisms were present in any of the smears. The cultures from the abdominal nodules gave rise to innumerable characteristic colonies of the organisms injected only.

The sections from the peritoneal nodules show small cavities enclosed in recent fibrous tissue; these cavities contain polymorphonuclear leucocytes, nuclear detritus, and the conidia of the organism in large numbers (Plate II., Fig. 8), most numerously just around the inside of the wall; here they are scattered about singly or arranged in groups; nearly all are extracellular, but intracellular groups occur. If the Gram stained sections be allowed to remain in alcohol for a little longer time than that just sufficient for decolorization then the organisms lose their stain largely and may appear as cocci or short, thick bacilli of various sizes. The organisms cannot be distinguished in the hæmatoxylin and eosin specimens. Giant cells are not seen in the interior of the abscesses, but in the recent fibrous tissue of the walls lies an occasional multinuclear cell of the tuberculous type. In a few places the appearances indicate beginning abscesses; the first effect of the organism is a necrosis of the tissue followed by cell accumulation; it cannot be made out clearly just how the organisms are carried, or go, from an older to a recent focus; the presence of bodies within cells, especially leucocytes, indicates that they may be transported by wandering cells; a few single bodies are found scattered about in the tissue outside of the abscesses.

Gray Mice. I. Intraperitoneal injection of 0.5 c.c. of a bouillon suspension produced death in two days. There was a purulent peritonitis, the organism being recovered from the exudate in pure growth. The internal organs were sterile and normal.

II. Subcutaneous injection of 0.5 c.c. was followed by death after two days. There were no special changes and the cultures remained sterile.

III. Subcutaneous injection of 0.5 c.c. was followed by evident symptoms of illness, ending in apparent recovery. The mouse died eighteen days afterward, but on account of beginning decomposition no cultures were made.

IV., V., VI. Subcutaneous injection of 0.5 c.c. Twenty days later one died, but the body was eaten by one of the survivors. This died two days later; there was some induration about the site of the inoculation, the tissues

being dry and shrunken. The cultures and smear preparations were negative. About this time the third mouse showed considerable shrinking about the injection—at the root of the tail; a small, dry ulcer formed, one of the extremities appeared fixed and rigid, so that the animal limped a good deal. It became thin, and died four weeks after the inoculation. The tissues about the ulcer were firm and fibrous; underneath the skin over the upper part of the right thighs and extending upon the under surface of the abdomen was a collection of whitish, viscid, caseous pus, which contained oval and oblong bodies in large numbers, and growing readily on glucose agar. The internal organs appeared normal both on gross and microscopic examination, and the smears from them did not show any organism.

White and Tame Mice. Four white mice were inoculated with 0.5 c.c of a forty-eight-hour-old bullion culture under the skin at the root of the tail. All reacted in about the same way. None died soon after the injection. In the second and third week they appeared to be getting thin. Beginning at the root of the tail and extending for a variable distance over the back there now formed a hairless, red area with an uneven surface; scattered over it would be occasional yellow spots. The posterior part of the body seemed more or less shrunken, the hind legs stiff, one often more so than the other; in one mouse the left posterior extremity seemed fixed and drawn up against the body. I killed one with chloroform on the twenty-third day, one died spontaneously on the twenty-sixth, one on the thirty-fifth, and the fourth on the fortieth day. In all there was found some undermining of the edges of the ulcerated surfaces described; the ulcer was superficial and did not extend into the muscles; at some points the tissues about the margins were firm and fibrous; where the skin was undermined small quantities of semi-solid cheesy material were found; sometimes such collections would extend for a considerable distance in the subcutaneous tissue; this material was composed largely of leucocytes, and among them were found, in varying numbers, organisms like the conidia of the fungus; in one animal there were numerous cocci also; in this case the cultures were mixed, most of the colonies being cocci, but quite a few colonies of the fungus developed. In all cases the internal organs were normal, with the exception of a possible enlargement of the abdominal lymph glands; no organisms were found in the smears, and the cultures remained sterile from the organs, which, including the lymph glands, were fixed in Zenker's fluid; the sections showed no changes, and organisms were not found in those stained by Gram's method or otherwise.

In order to study the evolution of the anatomical changes produced by this organism, four tame mice were injected simultaneously into the abdomen with 1 c.c. of a bouillon suspension of the same culture and killed at successive intervals of one week each. At the end of the first week a number of small nodules the size of a pin-head had developed near the site of the injection and in the omentum near the spleen, which was adherent to the stomach; the retroperitoneal glands were not enlarged; the cultures from the nodules remained sterile; the sections (Weigert, hæmatoxylin, etc.) of

the nodules show accumulations of cells with marked nuclear fragmentation and the formation of fibrin, especially at the periphery; scattered about are oval and lanceolate organisms, often in groups of four to six more.

At the end of the second week there were found nodules, a little larger, scattered principally over the peritoneum of the scrotal pouches. Cultures successful. Sections show the nodules to consist largely of a cellular granulation tissue, with smaller foci of marked nuclear disintegration, containing a much larger number of organisms than the nodules of a week's duration.

The third mouse died spontaneously on the twentieth day after the injection. There was a small ulcer over the lower part of the abdomen, and innumerable yellowish areas and more diffuse flat thickenings, with distinct spots of viscid softening over all parts of the peritoneum, the under surface of the liver, etc. Cultures successful. The sections show the tissue to be more fibrous, while the foci of softening contain granular and amorphous detritus, small nuclear clumps, and innumerable organisms often aggregated into heaps which appear as blue spots visible to the naked eye. In none of these or in any of the animals were fungous threads found in the lesions.

The fourth died spontaneously and was eaten in the abdomen by another mouse in the same cage.

There can therefore be no question but that the spore-forms multiply in the lesions they produce in susceptible animals.

Pigeons. Subcutaneous injections in two white pigeons of 2 c.c. of bouillon cultures did not produce any lesions or symptoms in three weeks.

There can be no doubt in regard to the identity of the organism described by Schenck and the one described in this article. The two correspond morphologically and culturally, and their pathogenic actions in animals are the same with the exception of a few easily explainable, insignificant differences. Schenck observed a general infection after subcutaneous injections in mice; as far as I know this did not occur in any of the animals that I used, and I obtained more decided pathogenic effects in guinea-pigs than Schenck seems to have done. These are difference that might reside just as well in the different races of animals used as in the organisms. In a personal communication Schenck states that on comparison the two organisms appear identical in form and in culture, Through the kindness of Dr. Schenck I was enabled to compare the two organisms, and I could not detect any distinguishing differences either culturally or morphologically. The injection of Schenck's fungus into the abdominal cavity of a mouse (December 5, 1899) was followed by death after four weeks, and the anatomical and histological characteristics of the lesions did

not differ in any essential from those of the lesions produced by the organism from Dr. Perkins' case.

It is regrettable that circumstances prevented the demonstration of the organism in the human lesions. More thorough study of the histological changes produced by the organism in man are also desirable. An abscess should be excised in an early stage of formation.

It is exceedingly interesting to note that we have here a pathogenic fungus that in the lesions it produces in animals exists in the spore-form, or in a modified spore-form, and that it undoubtedly multiplies as such; threads do not seem to develop in the tissues of susceptible animals. The exact manner in which the spores reproduce themselves under these circumstances I have not attempted to determine.

The fungus produces a slow, circumscribed, and nodular inflammation with necrosis and pus formation in the centre and the development of granulation and fibrous tissue at the periphery—encapsulation. This is seen especially well in the abdominal cavity of white rats and mice. The destruction of tissue after subcutaneous inoculation in mice may be quite extensive, large ulcerated surfaces with undermining and purulent infiltrations at the margins being the result. In less susceptible animals, such as the dog, dense areas of scar tissue are produced.

A characteristic clinical feature of the human cases is the refractory nature of the subcutaneous abscesses. This was pronounced in both Schenck's case and in the case under Dr. Perkins' care. Brayton[1] describes a similar case clinically; it occurred in a healthy young florist who punctured a finger with a wire while making bouquets; a succession of chronic abscesses with gelatinous contents appeared, extending during a period of two months from the finger to the elbow, much scarring being left behind. This case was not examined bacteriologically.

The three cases have much in common; in all a succession of similar, refractory, small abscesses of the upper extremity developed consequent upon injury by similar means; in Schenck's case the scratch of the skin of the finger by a nail; in Perkins' case the blow upon the finger by a hammer; and in Brayton's case the puncture of a finger by a wire.

[1] Indianapolis Medical Journal, 1899, xviii. p. 272.

FIG. 1.

FIG. 4

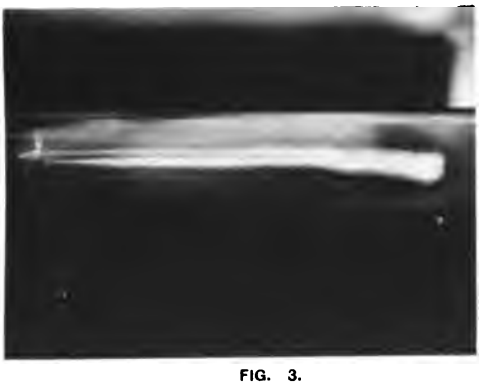

FIG. 3.

FIG. 2.

PLATE I.

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FIG. 5.

FIG. 7.

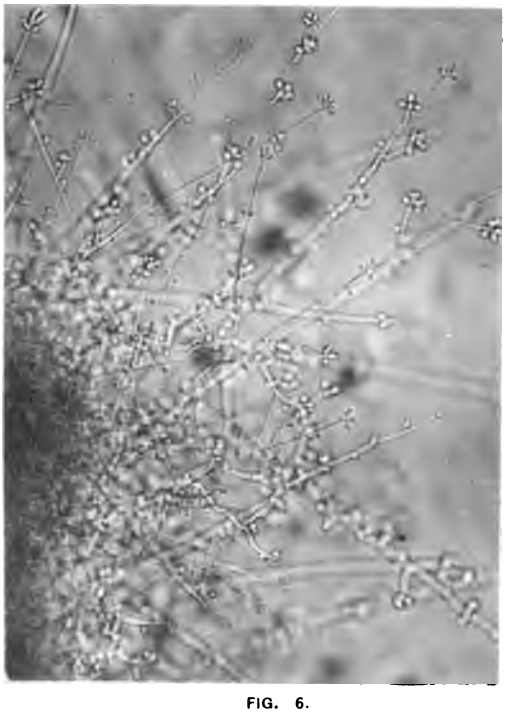


FIG. 6.

FIG. 8.

PLATE II.

DESCRIPTION OF PLATES I. AND II.

PLATE I.

FIG. 1.—Photograph of arm of patient, showing ulcers and scars, at a late stage of the lesions.
FIG. 2.—An original culture of the sporothrix, three weeks old.
FIG. 3.—Slant culture on glucose agar, four days old.
FIG. 4.—Slant culture on glucose agar, eight days old.

PLATE II.

FIG. 5.—Colonies on glycerin agar plate, forty-eight hours old.
FIG. 6.—Margin of living hanging-drop culture (gelatin). × 150.
FIG. 7.—Same as Fig. 6. × 1000. Unstained living culture.
FIG. 8.—Photograph of section of abdominal nodule in white rat. × 1000. Gram's stain. Cells and spores, the latter oblong and deeply colored.

DISCUSSION.

DR. FLEXNER: I have followed Dr. Hektoen's remarks and lantern demonstration with much interest, and from them I have little doubt that the micro-organism which he described is identical with that described by Dr. Schenck.

The study of the micro-organisms isolated from refractory subcutaneous abscesses by Dr. Schenck was carried out under my observation, so that I had the opportunity of following the details of his investigation. In comparing the observations made by Dr. Schenck with those of Dr. Hektoen I find that in so far as they have made common experiments there is but one difference—namely, the successful production by Dr. Schenck of a general invasion of micro-organisms in white mice. These animals were inoculated subcutaneously with suspensions made in bouillon. Death occurred on the sixth to the tenth day.

Smear preparations from the seat of the inoculation showed abundant oval and long forms of the micro-organism; and similar organisms were obtained in smears from the lungs and liver, but in smaller numbers. Cultures from the local lesions, lung and liver, gave pure growths. The organisms were not recovered from the kidney and from the heart's blood.

Microscopical examination of the tissues showed numbers of organisms in the liver, lung, and spleen, but the most strikingly characteristic appearances were found in the lymphatic glands, where the organisms were readily demonstrable in the peribronchial, perinephritic, and peritoneal glands, which contained them in immense numbers. They occurred for the most part outside of and between the lymphatic cells, although at times they were seen within the cells.

DR. DA COSTA: I would like to say a few words about the therapeutics of actinomycosis. In a case of the kind that has come under my observation iodide of potassium given in large doses had an admirable effect, and that is what the veterinary surgeons use. I think the disease, in the early stages, can be checked, and perhaps entirely cured. The case I refer to was one where the lungs were involved, but whether the treatment would succeed equally well in cases in which the liver or spleen is involved I do not know.

DR. HEKTOEN: In answer to Dr. Flexner's statement, I would like to say that I have attempted to produce septicæmia in mice with my organism, but so far have not succeeded. That is the only point in which this organism differs from the one described by Schenck.

GRAVES' DISEASE WITHOUT EXOPHTHALMIC GOITRE.

By WILLIAM H. THOMSON, M.D.,
OF NEW YORK.

THE statement that Graves' disease may exist and run its course without any sign of implication of the thyroid gland or of exophthalmos can be substantiated only by first showing that, beside the goitre and exophthalmos, the other symptoms of the disease form a group so definite and specific that they are sufficient of themselves to establish the diagnosis. We would, therefore, begin with a brief summary of those other symptoms to demonstrate that no different affection presents any such clinical picture; and hence, if we find the same picture exactly reproduced both in its chief and in its minor details, we must conclude that no other but Graves' disease can be present, even though the two striking objective symptoms of enlarged thyroid and eye protrusion be entirely absent. Such a demonstration, we think, is further important if it tends to prove that the cases without exophthalmic goitre are not incomplete or undeveloped cases of the disease, for I think it can be shown that in the respects of number, duration, severity, and fatality they are fully equal to those accompanied by goitre and exophthalmos. If sufficient clinical data can be produced to establish this fact, then exophthalmic goitre is no more essentially related to Graves' disease than hæmoptysis is to pulmonary phthisis. It is a common symptom, and no more.

The first of these specific symptoms of Graves' disease is the tachycardia. To be characteristic, it should range above 100, should be chronic and persistent, always present at every examination, through months and it may be years, and entirely independent of any other cause of tachycardia. These postulates would exclude cases of rapid action of the heart from nervous excitement, for such are not per-

sistent; also from anæmia and debility, for these are controlled by rest; also febrile tachycardia, for the temperature should be normal; also inflammatory or other organic derangements of the heart itself, because these also should be absent; also tachycardia from chronic cerebro-spinal affections, for there should be no signs of such states; and, lastly, the tachycardia of some patients with kidney disease, for in the great majority of these cases the kidneys are unaffected. After all such causes of rapid heart-action have been excluded it will be found that the marked tachycardia of Graves' disease is evidently specific, because not only can it be ascribed to nothing else, but its independence of them all shows that it is due solely to its own single special cause without the participation of any other element or condition. This fact about it is further emphasized in its being almost invariable. I found it absent only twice in the sixty-seven cases of my present report. The first is a patient with goitre but without exophthalmos, and which I would not exclude because of the presence of other characteristic signs. The second is a case without goitre or eye-change, but with tremor and other characteristic symptoms, and she has a sister with pronounced exophthalmic goitre. Both these cases are of recent origin comparatively, and the tachycardia may not yet have had time to develop. I need only add that sometimes the pulse falls below 100 shortly before death or in conditions of dangerous exhaustion from the disease, but then it is only a sign of approaching collapse and heart failure. Otherwise it may be termed the most persistent of all forms of tachycardia, generally the first symptom to develop and the last to disappear.

To be ranked next to the tachycardia are the characteristic nervous symptoms. These are both sensory and motor, but their great variety does not interfere with their significance as characteristic signs of the disease because they are grouped in a fashion found in no other malady. Among affections of the special senses may be mentioned pain in the eyes, amblyopia and diplopia and scotoma or colored spectra, or transient blindness almost invariably of only one eye. In the ears a sense of throbbing or fulness, transient but sometimes persistent deafness, tinnitus and severe aural vertigo; of smell, anosmia. Other nervous symptoms are insomnia and general nervousness closely resembling that accompanying fear or fright; mental depression, most marked in the morning and diminishing in the evening. A peculiar

irritability of temper, also as terminal mental symptoms, delirium, or mania. Other sensory symptoms are also very characteristic: shifting pains, causing stiffness, with tenderness of muscles, and often mistaken for rheumatism, frequent in the muscles of the neck; generally more on one side and extending up to the ear. A very curious pain which I have found in no other disease is a peculiar sensitiveness to touch of the auricle, sometimes of both ears, but generally of one, and quite persistent. Pains at the tips of the fingers and toes; pain in the heels. Cutaneous itching, shifting in site, is also common. Headaches of a migrainous type are very common. Of the motor symptoms, tremors are the most characteristic and greatly resembling trembling from emotion or fear, felt by the patient as inward and observable by others in voluntary movements, particularly of the right hand. These tremors are characteristically worse in the morning and less in the evening, so that many patients cannot write till evening. Weakness of the voice also, like that produced by emotion, but much more persistent. Weakness of the knees is very characteristic, and likewise abasia from their sudden giving way. Transient motor paralyses also occur, particularly of the seventh nerve or in separate branches of it.

Equally with the nervous symptoms, if not more characteristic of the disease, are the peculiar disorders of the digestive functions. These are generally among the earliest symptoms of which the patient is cognizant, and absent at the beginning of the history in only three out of my sixty-seven cases. They are both gastric and intestinal, and in neither case accompanied by any signs of an inflammatory or subinflammatory character. The gastric symptoms are anorexia with flatulence, often very troublesome and obstinate; nausea, and as a terminal symptom uncontrollable vomiting. The intestinal symptoms are an ill-defined feeling of distress through the bowels with prostration, even after natural movements, frequent constipation, but still more frequent diarrhœa, which generally occurs without apparent cause, is painless, watery, and devoid of mucus, and not particularly offensive. Nocturnal palpitation and morning mental depression very commonly accompany the diarrhœa. Nutritive disorders are emaciation, the rule in chronic cases, and often extreme. Loss of hair is very characteristic, so are sweatings and irritability of the bladder, especially at night.

As the disease progresses muscular weakness becomes extreme. The mode of death is strikingly uniform, usually by syncope.

Such being in brief the most common clinical developments of Graves' disease, I submit the following statistical comparison of their occurrence in thirty-three cases with exophthalmic goitre and in thirty-four without exophthalmos or goitre, all seen by me in my private practice or in consultation with other physicians, my notes beginning with the year 1888. I might add a number of others from my hospital experience, but for the fact that in this chronic complaint hospital patients rarely remain there long enough under observation:

Cases with goitre, 29 females, 4 males; cases without goitre, 27 females, 7 males.

Tachycardia present in the cases with goitre, 31; absent, 1. Without goitre, present, 33; absent, 1. General nervousness in those with goitre, pronounced in 18, common in 7, absent in 7. In the cases without goitre, pronounced in 17, and particularly in 5 patients, who were males. Two of these men spoke of it as simply maddening when it came on in paroxysms. In only 2 of the 12 female patients with this symptom very pronounced could this nervousness be said to resemble hysteria at any time. In the remaining 15 patients without goitre the nervousness was occasional in 8 and absent in 7.

Tremor was present in the 33 cases; with goitre in 26, not stated in 3, absent in 4.

Tremor in the 34 cases without goitre was present in 23, of whom in 16 it was severe, and intermittingly present in 7. The right hand was specially affected in 7. In every case the tremor was severe in the morning, and in several passed off altogether in the evening. In 1 case it did not develop till nearly two years after the tachycardia and the other symptoms, and then began in the tongue, followed by the hands and legs.

Tremor in the cases without goitre was absent in 6; not stated in 3.

Tremor of the eyelids on closing was the most constant symptom of all, being present in every one of the cases with goitre and absent in only 1 of the cases without goitre.

Pains in the cases with goitre, in the tips of the fingers and toes, in 5. In 3 mentioned as severe in the teeth. In 11, in the arms and legs. In 5, referred to the region of the heart. In 10, in the muscles of the neck—3 on the right side, 7 on the left side. Tender-

ness to pressure of the auricles, 8 times; deeper in the ear, 4 times. Pains were three times more frequent in the left ear than in the right.

In the cases without goitre, 7 complained of pain at the finger-tips and toes. In 5, in the heels; in 10, in the arms and legs. In 7, referred to the region of the heart; in 16, in the muscles of the neck—13 on the left side and 3 on the right. Tenderness to touch of the external ear was present in 14; in 9 the left auricle was exclusively affected; in 2, both were equally affected, and in 3 it was the right auricle alone.

Pains were not complained of in 12 out of the 34 cases without goitre. Pains in the eyes, 18 times with goitre, 14 times without goitre. Transient blindness of one eye; once in a case without goitre.

Deafness, more or less transient, was complained of in 8 of the cases with goitre; in 6 in the left ear, in 2 in both ears.

Deafness in one ear was present in 11 cases without goitre—in 5 of the right ear, in 6 of the left.

Severe vertigo was present in 4 of the cases with goitre, in 6 without goitre. Abasia in 6 cases with goitre, in 4 without goitre.

Falling of the hair—in 12 cases with goitre, in 8 cases without goitre. Sweating—14 times in cases with goitre, 8 times in those without goitre.

Irritability of the bladder—14 times in the goitre cases, 11 times in the non-goitrous.

Itching—8 times in the goitrous, 4 times in the non-goitrous.

Now, as we have remarked before, these cases without goitre cannot properly be classified "latent" Graves' disease, because the malady not only presents clinically just as severe a set of symptoms and conditions, but, in my experience, it has ended fatally in a greater number of those without than those with goitre, and no disease which is the sole cause of death should be called latent. The proper term, then, may rather be "unrecognized" than latent, and is another proof of the disadvantage of naming a disease after symptoms. I suppose everyone of us is familiar with instances where the presence of tabes was for long unrecognized simply because locomotor ataxia was but little pronounced.

This comparison of the clinical symptoms of these two classes of patients seems to me to show that those without exophthalmic goitre suffered from the same disease, and from no other disease, as those

who had exophthalmic goitre. The correspondence between the two classes in every essential particular in the course of the malady, as well as the same ratio in both of peculiar symptoms or accompaniments, cannot possibly be ascribed to coincidence or to accident. (See above.) This conclusion is also further borne out by the very late occurrence of exophthalmic goitre in several of these patients, and not until after they had suffered for many months with all the symptoms, and conversely by the disappearance of the goitre for a like prolonged period in others, while the disease continued as severe as ever, and in one case terminated in death without the nature of the complaint being diagnosed, simply because there was no goitre present, its existence three years before having been admitted to me at my visit, the patient being then first questioned about it. Lastly, the thyroid enlargement varies greatly from time to time without any appreciable change in the conditions accompanying the goitre in those patients who do have it, thus showing that it has none of the characters of a constant element in the complaint.

Another conclusion which my own experience has led me to hold strongly is that Graves' disease is a much more common complaint than is usually supposed. Owing to its protean symptoms, such patients are often wrongly diagnosed as cases of hysteria, neurasthenia, neuralgia, rheumatism, dyspepsia, chronic diarrhœa, etc., and most unavailingly treated accordingly.

On the other hand, a further proof that we are not justified in regarding the cases without exophthalmic goitre as incomplete or undeveloped Graves' disease is conclusively shown by the entire want of dependence of the severity of the affection or the presence or the extent of the thyroid enlargement. A number of these cases with pronounced goitre suffered much less from the other symptoms than those who never had any goitre at all. In my list three, and probably four, cases died of the disease without goitre, while only one died with the goitre and exophthalmos developed.

The bearing of these facts on the pathology of the complaint is obvious in one particular at least, and that is, that if hypertrophy of the thyroid gland is not a necessary part of the characteristic course of the disease it may not be a necessary factor in its pathology. In other words, affection of the thyroid gland is a frequent accompaniment, but not an essential element, in the disease. Instead, the

thyroid gland in Graves' disease is simply behaving like any other gland in that its secretion is not spontaneous or primary, but, like the parotids in salivation, it responds to the presence of a stimulus in the blood which leads to both its hypertrophy and its hypersecretion. That thyroid hypersecretion may of itself cause some of the symptoms of Graves' disease may be admitted without admitting that such hypothetical hypersecretion is the *causa causans* of the malady itself. That in those instances in which there is no palpable enlargement of the thyroid or any other signs pointing to the thyroid being any more affected than the parotids, or the spleen, that there is, nevertheless, a latent hypersecretion sufficient to cause even death is a perfectly gratuitous assumption.

But as it is not my present purpose to discuss the pathology or treatment of Graves' disease, I will simply close by saying that the demonstration of Graves' disease frequently developing without exophthalmic goitre is a fact that points elsewhere than to the thyroid as the primary source of the train of morbid symptoms, and that the marked influence which diet has upon the symptoms as distinctly points to the alimentary canal as the original seat of the developments which finally set up widely distributed processes of intoxication, of which irritation of the thyroid is only one of its many different effects.

DISCUSSION.

DR. EDES: I would like to ask Dr. Thomson whether he has noticed, among the other symptoms he has analyzed, an excessive sense of heat, so that the patient constantly complained of great discomfort in rooms which were of a temperature at or even below that found agreeable by other persons?

DR. THOMSON: Yes, that does occur, and I have seen it together with a complaint of itching.

DR. JANEWAY: I would say that I regard that symptom as one of the most constant symptoms of Graves' disease; it is nearly always present.

DR. A. MCPHEDRAN: I desire to draw attention to the fact that in many of the cases in which exophthalmos is reported to be absent, with the emaciation that usually occurs, there is no corresponding sinking of the eyes, show-

ing that there is after all some degree of exophthalmos. Such was the condition in two cases under my observation within the last three months. In both of them exophthalmos was reported as absent; but although there was considerable emaciation, there was no sinking of the eyeballs, and the palpebral fissures were wider than normal, showing an undoubted exophthalmos of slight degree.

DR. THOMSON: My attention has not been called to this condition.

NATURE AND DISTRIBUTION OF THE NEW TISSUE IN CIRRHOSIS OF THE LIVER.

(PRELIMINARY COMMUNICATION.)

BY SIMON FLEXNER, M.D.,
OF PHILADELPHIA.

MUCH has been written upon the histological changes of the liver in cirrhosis. The main attention, however, has been paid to the problem concerning whether the interstitial elements or the liver cells are primarily affected. Hitherto it has been deemed sufficient to speak of the increased interstitial tissue simply as connective tissue. The introduction of specific stains, especially in the last two years, for demonstrating elastic tissue has made it possible to determine what part of this so-called connective tissue is of the nature of the former tissue. The application, moreover, of certain dissociating technical methods previously employed in purely histological studies to the elucidation of the same problem has also led to the further differentiation of the several tissues concerned in the production of the "fibrosis" of cirrhosis.

That white fibrous tissue is contained in the human liver, especially in the interlobular spaces, has of course been known for many years, but that reticulum is also a regular constituent of this organ and permeates the lobules, we have come to know since the studies of digestion by Mall (*Johns Hopkins Hospital Reports*, vol. i., p. 171). We may, however, say that, so far as the technical methods are capable of indicating at this time, there is evidence of the occurrence of the three several kinds of connective tissue—white fibrous tissue, elastic tissue, and reticulum—within the liver, but that the distribution of the tissues varies. The ordinary white tissue is found with the bloodvessels, being therefore chiefly marked

and in the largest quantity in the interlobular spaces. Reticulum, on the other hand, occurs especially within the lobule; the fibrils are fine, and not usually demonstrable in stained preparations. The elastica, on the other hand, in the normal organ is present chiefly within and about the bloodvessels. It occurs also, as will be seen, in Glisson's and the surface capsules, as well as in the bile ducts.

The quantity of elastic tissue varies with the age of the individual. In children it is present in less amount than in middle age, and in the latter it is less abundant than in old age. The chief elastic tissue is contained in the bloodvessels and in Glisson's capsule, but it is found in the hepatic vessels and their branches, with the exception of the central veins, where it is usually absent, or, if it occurs at all, is present in very small amount.

The hepatic arteries and portal veins contain a well developed elastic membrane in the adventitial coats, the fibres composing the network being quite uniform in size. The muscular coats, especially of the arteries, are relatively free from fibres. The bile ducts, on the other hand, are distinguished from the bloodvessels, inasmuch as the layer of elastic tissue in the wall next the epithelium consists of a very delicate fibrillar network, while in the external layer, which corresponds with the adventitia of the bloodvessels, a thicker network occurs. A cross-section through the interlobular vessels shows that the elastica of the external layer of the portal vein, hepatic artery, and bile ducts unite into a network which surrounds, as a general capsule, the interlobular vascular system. Neither the outer nor the interlobular capsule sends elastic fibres into the interior of the lobules. The stroma of the lobules in normal organs consist solely of collagenous tissue.

Our knowledge of the distribution of the elastic tissue in the liver, both in health and in disease, we owe to the studies of Melnikow-Rasnednekow (*Ziegler's Beiträge*, xxvi., 1899, p. 526). The studies made by him upon such pathological conditions as atrophy, chronic congestion, and cirrhosis have led him to conclude that in chronic morbid hepatic processes associated with an overgrowth of connective tissue, this element is chiefly composed of elastic tissue. In simple atrophy of the organ the elastic tissue develops in the periphery where the atrophy usually begins.

Cirrhosis—atrophic, mixed, and hypertrophic—give rise to various

grades of the new formation of elastic tissue, depending upon the degree of the atrophy, the duration of the process, and probably its nature. More elastic tissue is found in the atrophic cirrhosis than in the mixed, and more in this than in the hypertrophic. The elastic tissue uses the interlobular vessels, especially arteries, portal veins, and bile ducts for its origination, but sometimes the hepatic veins are employed. The elastic elements grow especially in Glisson's capsule, but sometimes they penetrate into the acini between the rows of liver cells.

The studies which shall be reported briefly in this paper were carried out in the Pathological Laboratory of the University of Pennsylvania by Drs. Hatfield and Goepp. They had for their thesis the determination of the nature and distribution of the newly-formed tissue in cirrhosis. Account was taken not only of the normal and pathological distribution of the elastic tissue, but equally of the white fibrous tissue and reticulum. Commonly the three tissues were followed in the same organ, and a comparison of the results of the use of special technical methods as applied to them was made.

METHODS OF STUDY. ELASTICA. Two methods are now open to use for the demonstration of this tissue, both being in the nature of specific stains: the first is that of Unna, in which orcein is employed, and the other that of Weigert, which employs a resorcin and fuchsin combination. The early experiments with Unna's method were very unsatisfactory, because it was found that the staining was irregular and inconstant. On the other hand, Weigert's method gave from the beginning a constant result; it was therefore employed to the exclusion of the former method.

In the study of the amount and distribution of the elastic tissue, recourse was had to the method of digestion, for the purpose of controlling the results obtained with Weigert's stain. Inasmuch as elastica quickly disappears under the influence of pancreatic digestion, that element could easily be eliminated, while the remaining connective tissues were retained in the sections, thus affording a check upon the perfection of the selective stain.

Reticulum. For the purpose of demonstrating the tissue within the lobules of the liver, the digestive method, as first introduced by Mall, as well as the modification of Spalteholz were utilized. By these methods both fresh and preserved tissues in sections are

digested in alkaline solutions by means of pancreatin, when the parenchymatous cells and the elastic tissue are completely removed. There remains behind a framework consisting of white fibrous tissue and reticulum. Mall has shown us what the normal intralobular distribution of the reticular tissue is. Comparisons are then easily made between the normal and the pathological condition as found in cirrhosis.

White Fibrous Tissue. In the study of the white fibrous tissue of the liver, stained sections, both before and after digestion, were employed. Beside the ordinary stains for that tissue, and the reticulum stains which also color it, the recent specific stain of Mallory was employed. The last staining method was found especially useful in demonstrating the fine fibrils of white fibrous tissue contained within the liver lobules; but inasmuch as this stain also colors the reticulum its use is somewhat more limited than could be wished; on the other hand, it apparently leaves the elastic fibres unaffected. Attempts were made to eliminate the white fibrous tissue by digestion in caustic alkaline solutions, but with very imperfect success.

ELASTICA. For the purpose of study of the pathological distribution of this tissue, well-marked examples of cirrhosis, both atrophic and hypertrophic, as well as specimens of the liver which macroscopically appeared normal, but in which a slight proliferation of cells in the interlobular tissue had taken place, were employed. In a case of nodular cellular new growth small accumulations of lymphoid cells occurred in the interlobular tissue. These foci of cells are usually quite small, and do not penetrate into the lobules. There is a very slight, indeed, almost unappreciable, growth of ordinary fibrillated connective tissue within the nodules. On the other hand, finer and coarser fibrils of elastic tissue appear among the cells. The larger the periportal space the coarser the fibrils that occur in the cellular nodules. In another specimen of localized interlobular increase in the connective tissue, in which, however, the new tissue is very poor in cells, there is a very marked increase in elastic tissue. This tissue forms a quite uniformly meshed network, surrounding the vessels and extending throughout the connective tissue growth. There is in this case almost no attempt to invade the intralobular tissue. In marked examples of

perilobular cirrhosis specimens stained for elastic tissue, and observed by the naked eye, present an insular appearance. The islands are pale in appearance, vary in size from a fraction of a lobule to several lobules, and are separated by dark lines of elastic tissue. Microscopic examination shows that these dark bands correspond partially with the hypertrophied strands of Glisson's capsule, some, however, proceeding from the surface capsule and extending into the liver substance.

The indentations of the surface correspond with these depressed masses of fibres. There is a continuation of the elastic tissue in the capsule with the invading processes within the liver substances. The fibres in the capsule are arranged in the form of a crenated and closely woven network. A similar structure is apparent in the continuations within the liver. Newly-formed and dilated bloodvessels, the walls of which are composed of such fibrillated tissue, are associated with the new growth. In some places the new tissue within the liver substance consists of very closely anastomosing bands, in the midst of which are remnants of liver lobules. Not all of this dense tissue stains sharply, but the sharply stained fibres have the same meshed and crenated appearance as is seen about the capsule, and they proceed from the walls of bloodvessels and bile ducts. In the specimen being described there are a fair number of so-called, newly-formed bile ducts ; these, it should be emphasized, differ from the normal bile ducts in that they present a very imperfect development of elastic tissue about them, or in that they may be entirely deficient of such fibres. It is evident from the specimens that much of the new growth of interlobular tissue is not, properly speaking, elastic tissue. The new formation of elastic tissue in this form of cirrhosis does not remain limited to the periportal tissues. Just as in this condition the ordinary connective tissue invades the lobules, so may the elastic tissue appear in that situation. The degree of invasion is variable, but in such specimens as I have examined, it is not common to find much new elastic tissue within the lobules, unless those structures have been more or less completely destroyed by the new growth of tissue. The elastic tissue penetrates along the line of liver cells, usually in the form of fine bands or strands. In an instance of perilobular cirrhosis in which there was much cellular infiltration and penetra-

tion of the small cells, in the form of nodules, into the lobules, fine, wavy and anastomosing fibrils of the elastic tissue were present within the intralobular cellular accumulations.

HYPERTROPHIC CIRRHOSIS. The changes in this condition, which will be described, are based upon a small number of cases in which the livers were markedly enlarged and the surface smooth or very slightly indented. The interlobular new growth is scantier than in the previous examples described. Weigert's stain indicates that much of this tissue is composed of elastica, which presents in the form of bands, composed of branching, anastomosing fibres, many of them starting from or reaching the surface capsule. Where indentations of the surface are present they correspond with these bands. The sections are cut up into irregular islands of pale color by the bands of blue-stained fibrils which proceed from the interlobular tissue. In addition to these grosser bands fine wavy lines extend into the lobules, subdividing those units into much smaller units, composed of a few liver cells or even single cells. The fibrils last described often suggest continuity with the reticulum and the capillary walls that exist between the rows of liver cells. This intralobular growth may be extremely fine and very diffuse, so that the impression is obtained that a large part of the increase in size of the liver is brought about by this intercolation. The very minute fibres come out with such distinctness as to suggest that they may have been drawn with a pen.

Reticulum. For the study of the changes in the reticulum, several different specimens of atrophic and two specimens of hypertrophic cirrhosis were employed. The fresh tissue was studied by Mall's method, and the hardened tissue by the method of Spalteholz.

ATROPHIC. In an extreme grade of this form of cirrhosis digested specimens show a very large amount of new tissue in the periphery of the lobules and an intralobular invasion of coarse fibrils derived immediately from the extralobular growth. Wherever the lobules have been greatly encroached upon the reticulum is correspondingly reduced in volume; but what remains has not necessarily undergone any change in arrangement and in the size of the individual fibrils. On the other hand, the ingrowth of white fibrous tissue would appear to take place in such a way as to utilize the arrangement afforded by the reticular fibres. At first sight it

might be supposed that the coarse fibres just mentioned are a modified reticulum, but serial sections show that they are connected with the peripheral new growth of tissue. The great difficulty of separating by chemical means reticulum and white fibrous tissue makes it impossible to say whether after all some of the coarser fibres within the lobules in this case may not be reticulum. What is, however, very important and should be emphasized, is that after digestion and the elimination of all the elastic fibres there still remains behind a large amount, indeed, apparently as large a volume as before, of collagenous fibrils.

In other specimens in which the perilobular growth is less marked than in the previous instance, interesting changes were made out in the reticulum. In these specimens there is little or no invasion from without. The architecture of the reticulum is preserved in its normal arrangement, but the individual reticular fibres are hypertrophied, the greatest degree of thickening occurring in the periphery near the thickened interlobular tissue. While equally hypertrophied fibres are also found well removed from the peripheries in the centres of the lobules, yet at the same time I prefer to speak guardedly with reference to their ultimate nature. I think it possible that the fibres have proceeded from the interlobular tissue, in which case they are not, *a priori*, to be regarded as reticulum. On the other hand, if these fibres are of the nature of white fibrous tissue they represent an intralobular invasion from the periphery, which ordinary methods would not expose. It should be mentioned here that the study of the finer intralobular growth of the connective tissue is likely to be much facilitated by the new staining method for fibrous tissue recently introduced by Mallory (*Journal of Experimental Medicine*, 1900, vol. v., No. 1).

HYPERTROPHIC. The limited number of specimens (2) which have been open to study will not permit of any far-reaching conclusions being drawn. The main alterations, as shown by these cases, consist of a much more moderate new growth of tissue in the periphery of the lobules and a finer invasion of the lobules than in the previous class of cases. The difference between the original reticular fibres and the newer fibres is easily made out by the relative coarseness of the fibres and by their arrangement. While in a general way they follow the arrangement of the reticulum, they are

in places so increased as to obliterate the original architecture, and, in addition, they come together in what might be termed centres, from which the fibres radiate in all directions. These stellate centres form a good index of the degree of lobular invasion.

White Fibrous Tissue. This tissue has been considered in two previous sections. All attempts to eliminate it from the preparations by means of caustic alkaline solutions were more or less unsuccessful. By exclusion of the elastic element, on the one hand, and the consideration of the reticulum on the other, the conclusion was reached that white fibrous tissue is a constant and abundant constituent of all forms of marked cirrhosis; that in certain very cellular examples it is present in small amount, and perhaps is exceeded by the elastic element; but, on the other hand, wherever fibrillated tissue is present to any extent, notwithstanding the presence of elastica in large amount, there is also present equally large or larger amounts of white fibrous tissue.

CONCLUSIONS. 1. In all forms of cirrhosis the white fibrous tissue is increased.

2. Along with the increase of white fibrous tissue there is a new formation of elastic tissue. This new elastic tissue is derived from pre-existing tissue in the adventitia of bloodvessels and the hepatic capsules.

3. Both white fibrous tissue and elastic tissue, in all forms of cirrhosis, may penetrate into the lobules. This penetration takes place along the line of capillary walls or follows the architecture of the reticulum. The chief distinctions between the histology of atrophic and hypertrophic cirrhosis depend upon the degree of extralobular growth and the freedom with which the lobules are invaded. In hypertrophic cirrhosis there would appear to be less interlobular growth and an earlier and finer intralobular growth.

4. The alterations in the reticulum, *per se*, consist, as far as can be made out at present, of hypertrophy rather than hyperplasia of the fibres. It is still uncertain whether any of the differential methods now in use suffice to distinguish between the reticulum and certain fibres derived from the white fibrous tissue of the periphery of the lobules.

DISCUSSION.

DR. F. C. SHATTUCK: In what sense does Dr. Flexner use the terms atrophic and hypertrophic cirrhosis?

DR. FLEXNER: I use the term atrophic to mean the small granular liver, and hypertrophic for the large smooth liver, usually with jaundice.

DR. SHATTUCK: The result of Dr. Flexner's studies does not seem to harmonize with clinical observation. The very terms "atrophic" and "hypertrophic" involve confusion. We see two distinct groups of cirrhosis of the liver: first, that with ascites and no jaundice; second, that with jaundice and no ascites. In one portal vein, in the other bile-duct obstruction is present. In the first group the liver may or may not be enlarged—in my experience it usually is so—in the second it is always enlarged. Dr. Flexner finds the new growth along the course of the bloodvessels in the second group. And yet it is the bile-ducts rather than the bloodvessels which seem to be compressed or obstructed.

ANEURISM OF THE ARCH OF THE AORTA, WITH RUPTURE INTO THE SUPERIOR VENA CAVA.

By ALFRED STENGEL, M.D.,
OF PHILADELPHIA.

Among the terminations of aneurism of the arch of the aorta, one of the rarest is that which occurred in the case that forms the basis of this report. Most of the recorded cases are analyzed in the paper presented before the Association in 1890 by Drs. Pepper and Griffith. An interesting case in which the condition was recognized during life was subsequently published by Dr. Alex. Bruce[1] in 1895. I venture to record the present case because its characteristic features permitted a recognition during the life of the patient, and because it further illustrated some points in the prognosis which the analysis of previous cases had made clear.

I am indebted for the notes of the case and the privilege of reporting it to Dr. W. O. Xander, with whom I saw the patient.

C. H., a German-American, aged thirty years, a teamster. Weight, 150 pounds. He used no alcohol, and smoked moderately. The family history was good; both parents living and well. He had two sisters and three brothers, of whom one is suffering from post-typhoid insanity. (Fig. 1.)

The patient had scarlet fever at four, and an attack of inflammatory rheumatism at twelve; at twenty-five a second attack, which lasted four months. He had gonorrhœa three years ago, and was treated irregularly by a druggist. The running kept up for eight weeks; since then he has had difficulty in passing urine. A month before the fatal illness he had another attack of rheumatism, which kept him in the house for three weeks. His doctor told him to go to work to get the stiffness out of his bones. He accordingly went to work, hauling pipes, and felt very tired all week, and had shortness of breath on going up stairs. There was no swelling of his feet. His appetite was good.

Present History. January 27, 1900. At 3 o'clock, while at work, he suddenly felt a dull pain in the chest and a choking sensation in his throat.

[1] Edinburgh Medical Journal, vol. xl., Part II., p. 896.

FIG. 1.

From a photograph of the patient taken a short time before his illness.

FIG. 2.

Appearance of patient after onset of the disease. The dark discolorations on the chest and shoulder are ecchymoses.

Immediately he began to swell, and was taken to his home, and Dr. Xander sent for at 5 o'clock. The pulse-rate was 90, temperature 96°, respirations 24. He complained of fulness and pain in the throat. His neck and face very much swollen and cyanosed. Examination of the throat was negative. At 10 P.M. the swelling and distention of the veins extended down over the clavicles; there was no pain, but very great restlessness; he complained of dryness and choking in the throat.

28*th*. No sleep. Temperature 95.4° (mouth), 99.5° (rectal), pulse 90, respirations 24 and labored, though the resonance was good over both lungs. The nose and ears were very much cyanosed. The veins on his forehead greatly distended, and there was free perspiration about his head. The lower half of the body was normal. Air hunger was marked. (Fig. 2.)

29*th*. Œdema and cyanosis have now involved the chest, both anteriorly and posteriorly to the waist line. Size of neck, eighteen and one-half inches. In health wore a sixteen collar. Choking became more marked. Thought he might strangle, so called in Dr. Roberts to intubate him. He suggested venesection.

30*th*. No sleep. Is not able to lie down. Neck measures nineteen and one-half inches. Opened cephalic vein and allowed twenty-one ounces of blood to flow out, which gave him considerable relief. Though no decrease in the size of the chest or neck, it was noticed that cyanosis was somewhat less marked.

31*st*. Dozed for a few minutes at a time sitting in a chair. Voided six ounces of urine. Bowels opened with calomel. Basham's mixture ordered.

February 1*st*. Temperature 97.4°, pulse 96; urine, ten ounces in twenty-four hours. Scrotum beginning to swell. Venesection (brachial), fifteen ounces. Œdema appears in both arms, right more than the left. Veins on back very prominent. Blue veins along the waist line fading away.

2*d*. Only sleeps a few minutes at a time in a chair. Complains of weight of scrotum. Went down stairs twice to wash.

3*d*. Swelling in arms increased; no œdema in feet. Size of scrotum is uncomfortable.

4*th*. Made deep puncture into scrotum and bandaged it tightly to hasten the flow of serum. Venesection, nine ounces.

5*th*. Says he feels better. Scrotum much reduced in size. Still dozing. Temperature 98°, pulse 100. Feet beginning to swell.

6*th*. Slept a few hours under chloral and potassium bromide, 10 grains each. Cannot lie down.

7*th*. Very restless during night, even irritable at times. No pain; right foot swells more than the left. Has headache. Urine, fourteen ounces.

9*th*. Temperature 99°, pulse weak, respirations 24. Appears to dream a good deal, but can readily be aroused and appears rational.

10*th*. Scrotum filling.

11*th*. Is very irritable; complains of sick stomach. Bowels open; no pain; wants to go down stair .

12*th*. Scrotum increasing in size.

13*th*. Very uncomfortable; walks constantly. Sleeps only when drugged.

14*th*. Slept poorly during the night. Complains of pain in scrotum, which measures eighteen inches in circumference. Vertigo. Urine, ten ounces. Bowels open. Temperature 100°, respirations irregular, average 26; pulse 120, and weak. Ordered potassium acetate.

15*th*. Œdema of scrotum extends into both inguinal regions. Painful. Scarification gave immediate relief, by relieving pressure in the lymph channels. Bowels open freely. Urine, seventeen ounces.

16*th*. Feels better. Scrotum much reduced in size. No pain; only dragging. Urine, eighteen ounces. Swelling increasing in both lower limbs.

18*th*. Basham's mixture. Passed eighteen ounces of urine. Bowels open freely. Says he feels comfortable; only a choking and fulness in the throat. Is tired of room, and wishes to go down stairs. Has been smoking, and is hungry. Complains of headache.

20*th*. Is getting restless; headache; pulse weak and easily compressible. Sits in a semi-conscious state a great deal, and talks wildly. Cheers up when aroused.

21*st*. Pulse 130, weak; temperature 101°, respirations 28 and labored, though he is able to take a long, deep inspiration. Was very restless during the night. Delirious when dozing. In one of these spells he tried to jump out of a window. Early in the morning came down stairs. Bowels moved three times; urine, twenty ounces. Scrotum very large again, and in right leg swelling extends a hand-breadth above the knee; in the right, almost up to the knee. Died in convulsion at 11.45 A.M. Conscious twenty minutes before his death.

I first saw the patient with Dr. Xander on January 31st. At that time I noted the extreme swelling of the neck, especially above the clavicles, and the œdema of the face, arms and chest as far as the lower thoracic or upper abdominal region. There was a sharp line of demarcation formed by the limit of swelling and by a zone of deep cyanosis and ecchymosis, which passed around the body a little below the ensiform cartilage. The superficial veins of the neck and upper thorax were greatly enlarged, but the deeper veins of the neck could not be seen or felt on account of the great œdema. There were several ecchymoses on the right shoulder. The lower half of the body and the legs presented a wholly normal appearance. The patient could not lie down, and suffered with great dyspnœa in any position.

Physical examination was somewhat difficult on account of the degree of œdema. The cardiac beat was vigorous, heaving and situated outside the mid-clavicular line in the sixth interspace. A second centre of pulsation was detected in the region of the right third interspace, but this was diffuse and feeble. It was best developed by having the patient lean forward so as to throw the thoracic contents against the anterior wall of the chest. There was no thrill. The radial pulses were nearly equal, the right seeming a little stronger than the left.

On percussion an area of dulness was found to the right of the sternum, extending from the second to the fourth ribs and from a line one and one-half inch beyond the right border of the sternum to the left side of the sternum. Below and to the left the dulness was continuous with that of the heart. The cardiac outlines were bounded above by the third rib, below by the seventh, and the extreme left limit was three-quarters of an inch beyond the left mid-clavicular line. Pulmonary resonance was normal on both sides. The liver extended from the sixth rib to within an inch of the umbilical line. The spleen could not be felt.

Over the area of dulness to the right of the sternum there was a murmur which was immediately recognized as having the peculiar characters of a venous bruit. It was contiguous, but much increased during ventricular systole. The diastolic portion was long and vibrating in character, the systolic short and rather harsh. Excepting for the peculiar humming character of the diastolic sound, the murmur did not differ greatly from the double murmur sometimes heard in aneurisms of the first part of the aorta or in aortic-valve disease. The murmur was transmitted to the right as far as the anterior axillary line, but scarcely at all to the left. It could not be heard much beyond the left border of the sternum. The systolic sound was distinct over the body of the heart, but the diastolic was scarcely at all transmitted in a downward direction. Abnormal phenomena were sought for in the arteries and veins of the neck and arms, but were wanting. The second sound of the heart was inaudible in the aortic region, and was only faintly heard over the pulmonary artery. The breath sounds were equal in the two sides, and fremitus was likewise equal. There were sonorous and sibilant râles and some subcrepitant crackles at both bases. Nothing abnormal was found in the abdomen.

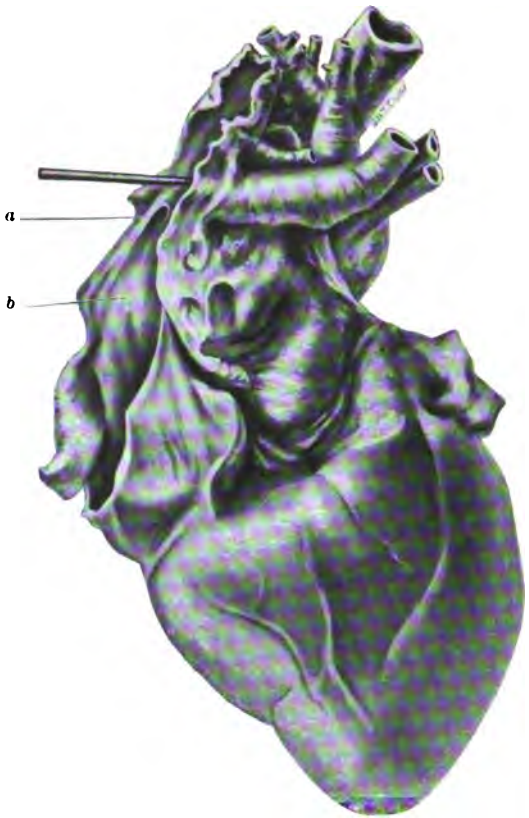
Autopsy. Body of a man, about five feet seven inches or eight inches in height. Enormous swelling above the waist line and very slight below the waist, the feet and legs to the knees and the scrotum being involved. The latter was discolored, the skin being a grayish-blue color, evidently in a state of beginning necrosis. There were several incisions in it, at the bottom of which grayish-yellow putrid tissue was visible. The swelling of the upper part of the body was found to be due to tense œdema, and the skin was of a mottled character, bluish in certain areas, and in some places showing distinctly enlarged veins. There were a number of incisions near the right shoulder, and about both arms where punctures had been made during life. On incision through the middle line the skin and subcutaneous tissues were found to be hard, and could be cut only with difficulty. Dark venous blood flowed freely from the incised tissues above the waist line. On close inspection it was found that the veins of the subcutaneous tissue were greatly enlarged, though flattened out by the pressure. They presented the appearances of the uterine sinuses, and the blood flowed in steady streams. Below the waist line the incision was entirely dry, as the incision is customarily at autopsies.

On removal of the sternum and ribs both pleural cavities were found to contain large quantities of serum, but this was particularly the case on the right side, where the effusion extended quite to the clavicle, and the diaphragm was depressed. The liver was pushed down and extended to within 2 or 3 cm. of the umbilical line. The lungs were considerably compressed and œdematous. On section frothy liquid flowed from the bronchi, and the substance of the lungs throughout was œdematous. After removal of the lungs, the azygos veins and intercostal veins were observed and found greatly enlarged. The large veins at the root of the neck could not be well identified, but were evidently enlarged, though bleeding from the subcutaneous veins had probably reduced their size, as the amount of blood lost in this way was very considerable. The pericardium was incised, and was found to be thickened, and the tissues in the region of the remnant of the thymus were especially œdematous and indurated. The appearance was that of a secondary sclerosis following long continued œdema.

The heart was found greatly enlarged, and its substance evidently quite flabby. The color as seen through the epicardium was decidedly pale and somewhat yellowish, and the course of the coronary vessels was marked by yellowish deposits of fat. On incision the substance of the left and right ventricles was found to be very soft, and the color grayish-yellow. The right ventricle was particularly affected, and the walls so much thinned and weakened that the papillary muscles could be distinguished from the outside as nodular areas of hardening. On incision into the chambers, fluid blood was removed, and the cavities on both sides were greatly enlarged. The tricuspid orifice was quite evidently dilated; the hand could almost be passed through this orifice without stretching it. The pulmonary orifice and artery were first laid open and the artery was apparently somewhat dilated, but otherwise normal. The aortic orifice was then opened and the valves were found to be stretched so that they were evidently incompetent. The sinuses of Valsalva were pouched, and the borders of the sinuses as well as the mouths of the coronary arteries were densely sclerotic.

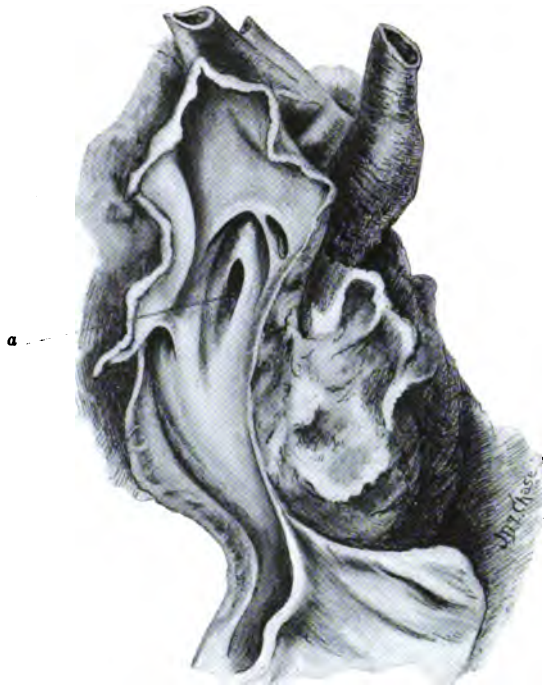
An aneurismal sac was discovered on the ascending portion of the aorta, extending toward the right. It was saccular in form, and about two and one-half inches in diameter. The endothelial lining was roughened and had atheromatous patches, especially in the upper and right side of the sac. There were a few soft clots within the aneurism, but nothing suggesting the formation of firm coagula. The sac compressed the superior vena cava from its entrance into the right auricle to the point of junction of the right and left innominate veins. The latter (left innominate) was somewhat compressed at its termination. The veins above the point of compression were greatly distended. (Fig. 3.) The aneurism was firmly attached to the vena cava, and a perforation was found in the latter just below the junction of the innominate veins. This communication was about a half inch in length and a quarter inch in width. The perforation occurred in the part of the aneurismal wall in which the atheromatous plates referred to were found. There

FIG. 3.



or view. The aneurism is concealed behind the pulmonary artery, the right auricle superior vena cava (*b*), which is opened to show the point of rupture (*a*). The probe to the innominate vein.

FIG. 4.



Lateral view, looking into the opened vena cava. The point of rupture is indicated at *a*.

had evidently been great thinning of the sac wall in this situation for some time prior to the time of rupture. (Fig. 4.)

The lungs were intensely œdematous, and on section a large amount of frothy serum exuded. In places there were small hemorrhagic extravasations.

The liver was congested, though not extensively. The structure was in other respects quite normal. The kidneys, spleen, and other abdominal organs presented no noteworthy features.

It was quite evident at the first examination of the patient that he was suffering with aneurism of the first part of the aorta, and it was also clear that the superior vena cava had become obstructed. The only difficulty in the case was the determination of the cause of the obstruction. It was possible that this might be due to a sudden dilatation (without rupture) of an aneurismal sac, or to a clot in the vein, or to the condition actually present—rupture of the aneurism. The fact that aneurismal sacs may suddenly expand under the influence of strains is of course well known, and it is easily possible that such a dilatation might bring about a sudden compression of the vena cava, with symptoms like these described. A continued venous bruit might further be caused by such a narrowing. In the second place, a slow thrombosis of the vena cava above a constriction caused by pressure of an aneurism could also terminate in complete venous occlusion by separation of the clot and its lodgement lower down in the narrowed part of the vein. In this case, however, the symptoms would be more likely to develop more slowly than was the case in our patient, though the immediate effect of such a thrombosis with secondary dislodgement would be a sudden obstruction of the cava. The possibility of aneurismal rupture causing symptoms such as were present is well illustrated in the thirty cases collected by Pepper and Griffith. Their analysis showed the principal diagnostic indications to be the following:

1. Cyanosis, œdema, coldness, and distention of the veins of the upper part of the body, with other evidences of obstruction to the circulation of the blood in the tributaries of the superior vena cava.

2. The suddenness of the onset of the symptoms.

3. Evidences from physical examination of the presence of a tumor in the thorax, and the probability that this is aneurismal.

4. The existence of a murmur characteristic of a communication between an artery and a vein.

These symptoms are sufficiently distinctive to establish the diagnosis, particularly if the last is well marked. The only difficulty in my own case was the fact that the humming diastolic portion of the murmur was not distinctive after the first examination, and during the remaining weeks of life did not differ greatly from the diastolic element of a murmur caused by an aneurism of the aortic arch with dilatation of the valve orifice or by simple aortic valve disease. One point of great significance was the right lateral transmission of the murmur and the absence of the murmur over the body of the heart, at the ensiform, and at the apex. Regurgitant aortic murmurs are so commonly propelled in these directions that it seemed clear that the bruit present in the case was of a different sort. On this ground the possibility of simple constriction of the vena cava by a sudden distention of the sac was excluded, and the humming murmur referred to a rupture rather than to a venous stenosis or aortic regurgitation. The autopsy showed the likelihood of the existence of some aortic regurgitation, but this had certainly not produced characteristic signs.

A matter of prognosis of interest is the probable duration of life and the possibility of cure. In the case of Damaschino and Lavin, in which recovery occurred, there is sufficient evidence to warrant the diagnosis, and a study of the specimen in my own case is convincing that recovery might occur. After the venous system has been engorged the backward and forward flow through the orifice of the rupture is apt to be much less than the location and nature of the lesion would make us imagine. Under these circumstances a clot might form that would obstruct the ruptured aorta. These considerations would lead to a thought regarding treatment, viz., that too active venesection may do injury by depleting the venous channels and thus restoring the strength of the systolic current through the rupture. Venesection should be performed when the danger to life is excessive, but ought to be moderate in the amount of blood taken.

As to the duration of life, the analysis of published cases establishes the surprising fact that some cases have lived for weeks and even as much as seven months after the rupture. In the case here reported the duration was twenty-four days, a long continuance considering the early severity of the symptoms and a further evidence of the possibility of occasional recovery.

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